Spreading Depolarizations: A Precision Medicine Approach to TBI Treatment

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Disclosures

• None
• Involved in NIH-funded clinical and basic science research projects focused on traumatic brain injury
Learning Objectives

• 1. Understand the challenges of clinical trials involving traumatic brain injury
• 2. Understand the importance of NIH/NINDS Common Data Elements
• 3. Explain spreading depolarizations (SDs) and their role in TBI
• 4. Understand how SDs contribute to a precision medicine approach to TBI
Since 2000

• Over 4000 preclinical studies on TBI
• Over 900 clinical trials
• Approximately 90 Phase 3 trials
• 0 successful therapeutic interventions
Failure of Animal Models?
Very Early Administration of Progesterone for Acute Traumatic Brain Injury

David W. Wright, M.D., Sharon D. Yeatts, Ph.D., Robert Silbergleit, M.D., Yuko Y. Palesch, Ph.D., Vicki S. Hertzberg, Ph.D., Michael Frankel, M.D., Felicia C. Goldstein, Ph.D., Angela F. Caveney, Ph.D., Harriet Howlett-Smith, R.N., Erin M. Bengelink, M.A., Geoffrey T. Manley, M.D., Ph.D., Lisa H. Merck, M.D., M.P.H., L. Scott Janis, Ph.D., and William G. Barsan, M.D., for the NETT Investigators*

“study. In addition to strict compliance with the study protocol, critical elements of TBI management were standardized across the study sites to minimize the effects of practice variability and secular trends. Adherence to both the study protocol and the TBI management guidelines of the trial were centrally monitored daily. Failures of
What went wrong?

Classification

GCS
(Glasgow Coma Scale)

Mild

Moderate

Severe

Outcome

GOS
(Glasgow Outcome Scale)

Death

Good Recovery

Vegetative
Modern disease classification is a mixture of anatomically physiologically, metabolomically, immunologically, and genetically defined diseases.
13 Study Sites

Washington
UCSF
UTSW
Baylor/UT Houston
Austin
Miami
Cincinnati
Pittsburgh
VCU
Maryland
Harvard
Penn

Many additional collaborative sites for data analysis; More sites being added
A New Taxonomy for TBI

• Not simply lumping by GCS
• Not simply using GOSE as measure of success
• Taxonomy to allow for patient targeted interventions
A Precision Medicine Approach

Genome
Proteome
Physiology
Clinical Data
Imaging
Symptoms

GCS

Headache
Depression
Fatigue
Memory
Dizziness

EtOH > 300
Na = 128

PctO2
ICP
EEG

UCH-L1
GFAP
S100B
Spreading Depolarizations (SD)
SDs as mechanism for acute cortical lesions

Global ischemia

Subarachnoid hemorrhage

Mild ischemia (endothelin)

EAAT inhibition

Focal ischemia

Traumatic brain injury
What are SDs?

- Self-propagating wave of near complete breakdown of hemostasis of ion gradients in neurons and astrocytes
- Near-complete sustained depolarization in individual neurons
- Neuronal swelling and distortion of dendritic spines
- Loss of electrical activity
- Causes brain electrical silence
SDs start with a noxious condition

- Mechanical injury
- Hyperthermia
- Acute hyperexcitability (status epilepticus)
- Hypo-osmolality
- Hypoxia and ischemia
- Chemical agent (potassium)
Spreading Depolarizations

Spreading Depolarization vs Depression

Spreading Depolarization
A self-propagating wave of abruptly developing, near-complete breakdown of transmembrane ion gradients in neurons and astrocytes *en masse* that spreads through contiguous cerebral gray matter at a typical velocity of 2–5 mm/min (range: 1–9 mm/min) and is locally sustained for at least 15 s. Depolarization can be recorded as a negative shift of the extracellular direct-current potential (frequency range <0.05 Hz).

Spreading Depression
A wave of depression in spontaneous activity of the electrocorticogram (>0.5 Hz) that propagates through contiguous cerebral gray matter at a typical velocity of 2–5 mm/min. **Spreading depression is a consequence of spreading depolarization.**

Spreading depolarization can occur without spreading depression (tissue with no spontaneous activity), but spreading depression is always caused by spreading depolarization.

Dreier et al., *JCBFM*, 2016 Jun 17 (in press)
Hartings et al., *JCBFM*, 2016 June 21 (in press)
Describes the wide spectrum of depolarization characteristics that can be observed depending on local tissue conditions. These characteristics include varying durations and metabolic responses.
Three requirements for infarction:
- ischemia
- depolarization
- persistence of both (time)
Ischemic core

- **NORMAL PERFUSION**
  - **OUTER PENUMBRA**
  - **CLASSICAL PENUMBRA**
  - **ISCHEMIC CORE**

**persistent depolarization**
(anoxic or asphyxial depolarization)

- 1
- 2
- 3

- altered spontaneous activity
- electrical silence
- $\leq 5-10 \text{ ml/100g/min}$
- $>5-10 \text{ and } <15-23 \text{ ml/100g/min}$
- $\geq 15-23 \text{ and } \leq 35 \text{ ml/100g/min}$

**Severe ischemia onset**

2-5 min

**Dilated lesion growth**

- **NORMAL PERFUSION**
  - **OUTER PENUMBRA**
  - **CLASSICAL PENUMBRA**
  - **EXPANDED ISCHEMIC CORE**

- **persistent depolarization**

- altered spontaneous activity
- electrical silence
- $\leq 5-10 \text{ ml/100g/min}$
- $>5-10 \text{ and } <15-23 \text{ ml/100g/min}$
- $\geq 15-23 \text{ and } \leq 35 \text{ ml/100g/min}$

**2-5 min**

Triggers of secondary spreading depolarizations

Susceptible to decrease in supply

Susceptible to increase in demand

SDs can spread into normal tissue

- SDs spread at rate of 2-6mm / min
- Associated hyperemia (markedly increased CBF)
- Mismatch of CMR of oxygen can lead to tissue hypoxia
Electrocorticography in Human Brain Injury
Electrode strip placement

**Ideal placement**
- Targets penumbra
- Lies along single gyrus

**Poor placement**
- Remote from injury
- Crosses major sulcus

**Key tips**
- Exit through burr hole
- Tunnel sufficiently
- Coil and anchor exteriorized lead
1. Place ground electrode on shoulder or scalp; reference (subdermal platinum needle) at mastoid or frontal apex

2. Connect electrode strip to cable

3. Plug electrodes into amplifier and begin monitoring

In the Intensive Care Unit
1. Negative direct current shift identifies depolarization
2. Depolarization causes depression of high frequency activity

Electrocorticography in patients

1. Compressed time scale (≥ 30 min / page)
2. DC or near-DC amplifier to record slow changes
3. Large amplitude signals
... vs. EEG

100 µV

1 sec
Electrocorticography in patients

Filter in slow activity

Compress time scale

Moberg CNS – Advanced ICU amplifier for COSBID

- 8 channels for ECoG
- Full-band DC amps (ECoG/EEG)
- New software for bedside SD detection
SDs in TBI Patients

- Occur in 53% of patients
- Peak within first 36hr
- Secondary brain insults associated with depolarizations
  - Yet also exist independent of other measurable physiological abnormalities

Depolarizations occur independent of other secondary insults

* GCS = 13
ICP = 13
CPP = 69
Temp = 37.7

Depolarizations occur independent of other secondary insults

<table>
<thead>
<tr>
<th></th>
<th>Number of SDs (patients)</th>
<th>Normal range</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>1,657 (54)</td>
<td>1,602 (97%) (&gt; 70 mm Hg)</td>
<td>55 (3%) (&lt; 70 mm Hg)</td>
</tr>
<tr>
<td>Intracranial pressure</td>
<td>1,226 (48)</td>
<td>1,196 (98%) (&lt; 20 mm Hg)</td>
<td>30 (2%) (&gt; 20 mm Hg)</td>
</tr>
<tr>
<td>Brain tissue oxygenation</td>
<td>510 (19)</td>
<td>393 (77%) (&gt; 20 mm Hg)</td>
<td>117 (23%) (&lt; 20 mm Hg)</td>
</tr>
<tr>
<td>Cerebral blood flow</td>
<td>234 (14)</td>
<td>165 (71%) (&gt;18 ml/100g/min)</td>
<td>69 (29%) (&lt;18 ml/100g/min)</td>
</tr>
</tbody>
</table>

See also Hartings et al., J Neurotrauma 26:1857-66, 2009
Detecting SDs with Intraparenchymal Electrodes

Jeffcote, et al. 2014. Neurocrit Care
Expanded Patient Population

ICP + PbtO2 + Temp

rCBF

dEEG
Detecting SDs with Continuous EEG

Spreading Depolarizations II: Development and validation of spreading depolarization monitoring for TBI management

• How wide spread are SDs in TBI?
  • Occur in patients with “mild” or “moderate” TBI?
• How can we monitor and detect SDs in real time?
  • Allow for real-time intervention
Multi-center Trial

• University of Cincinnati – coordinating site
• PI: Jed Hartings, PhD
• Study Co-I: Brandon Foreman, MD; Opeolu Adeoye, MD; Geoffrey Manley, MD, PhD
• 6 TRACK-TBI Sites
  • UC, Baylor, Univ Miami, Univ Pittsburgh, MGH, UCSF
• UC Site PI: Laura Ngwenya, MD, PhD
• UC Co-I: Norberto Andaluz, MD; Opeolu Adeoye, MD
SDs as risk factor for worse outcome?

• SDs are known to be associated with aura of migraines

• Are some patients at risk for worse outcomes because brain predisposed to SDs?

• Can identification of patients with SDs lead to better therapeutic options?

Treating Spreading Depolarizations

• No clinical trials yet to assess feasibility and efficacy of treating SDs in patients with TBI
• NMDA receptor antagonists show promise
  • With SD: Surge of extracellular K; intracellular Na and Ca increase → glutamate release
  • Glutamate induces NMDA receptor activation → contributes to SD initiation, propagation
Clinical anecdotes show ketamine stops SD

Ketamine decreases incidence of SDs in brain injured patients

A Precision Medicine Approach

Genome
Proteome
Physiology
Clinical Data
Imaging
Symptoms

GCS

UCH-L1
GFAP
S100B

EtOH > 300
Na = 128
Hct
ICP
EEG

Fatigue
Memory
Dizziness
Depression
Headache

Agitated
10mmHg
Conclusions

• A “cure” for TBI requires a precision medicine approach
  • Defining the target patient
  • Defining the intervention
  • Defining the outcome measure

• Spreading depolarizations are periods of abnormal electrical activity that contribute to cortical ischemia and infarction

• Patients with SDs may represent a patient population that can be targeted for specific intervention

• The ability to identify SDs in patients outside of the severe TBI spectrum will help to better understand how SDs contribute to the pathology of TBI and lead to additional therapeutic interventions
Documentary
History and Perspectives on Spreading Depolarization Monitoring in the Clinic

Moberg YouTube channel:
www.youtube.com/watch?v=JbhTbtxWaSo
Hartings et al., The continuum of spreading depolarizations in acute cortical lesion development: examining Leão’s legacy. 2016 Jun 21 (in press)

Dreier et al., Recording, analysis, and interpretation of spreading depolarizations in neurointensive care: review and recommendations of the COSBID research group. 2016 Jun 17 (in press)
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