Overview of Therapeutics for TBI

Edward D. Hall, Ph.D.
Director, University of Kentucky Spinal Cord & Brain Injury Research Center
Pathophysiology of and Treatment Approaches for Traumatic Brain Injury

• **Primary Injury** - Mechanical shearing of axons and blood vessels: can only be improved by
  - Enhancement of axonal plasticity‡: axonal sprouting and formation of new synapse
  - Formation of new blood vessels

• **Secondary Injury** - Microvascular and neuronal injury due to a cascade of pathophysiological events that exacerbate primary injury.
  - Potential for pharmacological neuroprotective treatments that interrupt secondary injury at single or multiple (combination strategies) target sites
TBI

- Petechial Hemorrhage
- Iron Release
- Depolarization
  - Voltage Dependent Channel Opening Na⁺, K⁺, Ca²⁺
  - Glutamate Release
    - NMDA and AMPA Receptor Activation

Intracellular Ca²⁺ Overload

- Mitochondrial Dysfunction
  - Energy Failure
    - Lactate

- NOS Activation
- AA Cascade Activation (COX1, COX2, 5-LO)
- Calpain Activation

Oxidative Damage

- Reactive Oxygen Formation (ONOO⁻)
- PGF₂α, TXA₂, LTs

Cytoskeletal Degradation

- Neuronal Damage
- Myelin Damage

Neurological Deficit

- Microvascular Damage
- Ischemia
TBI

AA Cascade Activation (COX1, COX2, 5-LO)
Seconds‡  Hours

PGF$_2$α, TXA$_2$

LTs

Microglial/Astrocyte Activation
Minutes‡  Weeks

Cytokine Release (TNFα, IL-1β, IL-6)

Monocyte Influx
Days‡  Weeks

Macrophages
Days‡  Weeks

Lymphocyte Influx
Days‡  Weeks

PMN Influx
Hours‡  Days

Amplification of Injury and/or Repair
Interactions of Glutamate Release, Ca^{++} Overload and Reactive Oxygen Damage in Secondary Injury

“Wheel of Mis-Fortune”

Glutamate Release → Glutamate Receptor Stimulation

Lipid and Protein Oxidation → Reactive Oxygen formation

Increased [Ca^{++}]i → Activation of phospholipases, Proteases (calpain) endonucleases, nitric oxide synthase

Neuronal Death

Modified from Pelligrini-Giampietro and Moroni, 1991
Compounds That Have Failed to Produce an Overall Improvement in Phase III (or large Phase II) TBI Trials

- **Nimodipine (Nimotop; Bayer)** - L-type Ca$^{++}$ channel blocker
- **Selfotel (CGS19755; Ciba-Geigy)** - competitive NMDA antagonist
- **D-CPP-ene (Sandoz)** - competitive NMDA antagonist
- **Aptiganel (CNS1102, Cerestat; Cambridge Neuroscience)** - non-competitive NMDA antagonist
- **CP 101,606 (Traxoprodil; Pfizer)** - non-competitive NR2B subtype selective NMDA antagonist
- **PEG-SOD (PEG-orgatine; Sterling-Winthrop)** - free radical scavenger
- **Tirilazad (U-74006F, Freedox; Upjohn)** - lipid peroxidation inhibitor
- **Dexanabinol (HU211; Pharmos)** - non-competitive NMDA antagonist/antioxidant/TNF$\alpha$ inhibitor
LACK OF EFFECT OF INDUCTION OF HYPOTHERMIA
AFTER ACUTE BRAIN INJURY

Guy L. Clifton, M.D., Emmy R. Miller, Ph.D., R.N., Sung C. Choi, Ph.D., Harvey S. Levin, Ph.D.,
Stephen McCauley, Ph.D., Kenneth R. Smith, Jr., M.D., J. Paul Muizelaar, M.D., Ph.D.,
Franklin C. Wagner, Jr., M.D., Donald W. Marion, M.D., Thomas G. Luerssen, M.D., Randall M. Chesnut, M.D.,
and Michael Schwartz, M.D.

Results The mean age of the patients and the type and severity of injury in the two treatment groups were similar. The mean (±SD) time from injury to randomization was 4.3±1.1 hours in the hypothermia group and 4.1±1.2 hours in the normothermia group, and the mean time from injury to the achievement of the target temperature of 33°C in the hypothermia group was 8.4±3.0 hours. The outcome was poor (defined as severe disability, a vegetative state, or death) in 57 percent of the patients in both groups. Mortality was 28 percent in the hypothermia group and 27 percent in the normothermia group (P=0.79). The patients in the hypothermia group had more hospital days with complications than the patients in the normothermia group. Fewer patients in the hypothermia group had high intracranial pressure than in the normothermia group.

Conclusions Treatment with hypothermia, with the body temperature reaching 33°C within eight hours after injury, is not effective in improving outcomes in patients with severe brain injury. (N Engl J Med 2001; 344:556-63.)
Contributing Factors to Phase III TBI Failures

• Inadequate understanding of secondary injury mechanisms, their time courses and their inter-relationships

• Inadequate preclinical testing
  – Lack of definition of BBB penetration, dose-response and therapeutic blood levels, duration of treatment and therapeutic window
  – Lack of testing in multiple models (e.g. diffuse vs. focal)

• Choice of mechanisms with short therapeutic windows

• Inadequate clinical trial design
  – Insensitive endpoints
  – Inclusion of all types of patients (i.e. lack of recognition of subgroups that might be likely to benefit from particular drug)
  – Long enrollment windows that probably exceed therapeutic window for the drug

Recommendations from NINDS-Sponsored Workshop on Clinical Trials in Head Injury, 2000

• Identify and target specific mechanisms of cellular injury
• Obtain adequate preclinical data (e.g. dose-response, therapeutic window, optimal duration of treatment, pharmacodynamic-pharmacokinetic correlation, multiple models)
• Focus trial on the appropriate subgroup of patients
• Confirm adequate delivery of drug to the brain
• Standardize clinical management across centers
• Choose the right outcome measures
• Use of surrogate outcome measures in Phase II, but not Phase III
• Statistical considerations
• Informed consent considerations
• Improve study management
• Seek FDA input early

There have been some hints of success in some trials with some drugs!
The Effect of the Selective NMDA Receptor Antagonist Traxoprodil in the Treatment of Traumatic Brain Injury

LORRAINE YURKIEWICZ, JERRY WEAVER, M. ROSS BULLOCK, and LAWRENCE F. MARSHALL

**Table 2. DGOS Favorable Outcome**

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th></th>
<th>Last visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CP-101,606, n = 177</td>
<td>Placebo, n = 199</td>
<td>CP-101,606, n = 198</td>
</tr>
<tr>
<td>Percent favorable</td>
<td>41.2</td>
<td>35.7</td>
<td>43.4</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>1.33 (0.85, 2.06)</td>
<td></td>
<td>1.47 (0.97, 2.25)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.21</td>
<td></td>
<td>0.07</td>
</tr>
</tbody>
</table>

aRaw percentages, i.e., n favorable/N randomized.
bOdds ratios and p-values from the logistic regression model adjusted for pooled center and baseline motor score.
DGOS, dichotomized Glasgow Outcome Scale; CI, confidence interval.

**Table 3. DGOS at Last Visit by Gender**

<table>
<thead>
<tr>
<th>Gender</th>
<th>n</th>
<th>Percentage favorable</th>
<th>(CP-101/Pbo)</th>
<th>CP-101</th>
<th>Pbo</th>
<th>Delta</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>298</td>
<td></td>
<td>(146/152)</td>
<td>46.6</td>
<td>35.5</td>
<td>11.1</td>
<td>1.73</td>
<td>1.07, 2.80</td>
</tr>
<tr>
<td>Female</td>
<td>106</td>
<td></td>
<td>(52/54)</td>
<td>34.6</td>
<td>37.0</td>
<td>-2.4</td>
<td>0.85</td>
<td>0.37, 1.93</td>
</tr>
</tbody>
</table>

aRaw percentages, i.e., n favorable/N randomized.
bEstimate of odds ratio (OR) and 95% confidence interval (CI) are based on a logistic regression model with the following terms: baseline motor score strata, treatment, gender, and treatment by gender interaction.
DGOS, dichotomized Glasgow Outcome Scale; Pbo, placebo.
A multicenter trial on the efficacy of using tirilazad mesylate in cases of head injury


Division of Neurological Surgery and Department of Family Medicine, University of California at San Diego, San Diego, California; The Executive Committee of the International Tirilazad Trial, Paris, France; and Pharmacia UpJohn, Kalamazoo, Michigan

- Significant reduction in mortality in severely injured males with traumatic SAH from 43-->34% (p<0.07)
- Also a reduction moderately injured males with tSAH from 24 to 6% (p<0.025)
• **Nimodipine (L-type Ca\(^{++}\) blocker)** - German phase III study (Harders et al. J. Neurosurg. 85:82-89, 1996
  • Reduction in GOS unfavorable outcome in tSAH TBI patients from 46.0% \(\downarrow\) 25% (p=0.002)
  • Meta-analyses of all nimodipine TBI trials is less convincing

• **Moderate Hypothermia (33 degrees C)**
  • Early hypothermia (i.e. on admission) may improve outcome
  • Lessening of ICP
Hypothermia Treatment for Traumatic Brain Injury: A Systematic Review and Meta-Analysis

KIM PETERSON, SUSAN CARSON, and NANCY CARNEY

Table 4. Relative Benefit of Improvements in Neurological Outcome for Hypothermia versus Control Treatments in TBI Patient Subgroups in Trials That Studied Comparable Groups

<table>
<thead>
<tr>
<th>Subanalyses</th>
<th>RR (95% CI)</th>
<th>No. of trials</th>
<th>N</th>
<th>$\chi^2$ (p-value)</th>
<th>$I^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooling duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooled up to 48 h</td>
<td>1.05 (0.82, 1.36)</td>
<td>5</td>
<td>601</td>
<td>7.51 (0.11)</td>
<td>46.8%</td>
</tr>
<tr>
<td>Cooled over 48 h</td>
<td>1.91 (1.28, 2.85)</td>
<td>3</td>
<td>179</td>
<td>0.30 (0.86)</td>
<td>0%</td>
</tr>
<tr>
<td>Target cooling depth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate depth</td>
<td>1.41 (1.04, 1.91)</td>
<td>5</td>
<td>608</td>
<td>7.49 (0.11)</td>
<td>46.6%</td>
</tr>
<tr>
<td>Mild depth</td>
<td>1.02 (0.61, 1.71)</td>
<td>3</td>
<td>172</td>
<td>5.82 (0.05)</td>
<td>65.7%</td>
</tr>
<tr>
<td>Rewarming strategy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive rewarming</td>
<td>2.05 (0.98, 4.31)</td>
<td>1</td>
<td>66</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Active rewarming</td>
<td>1.19 (0.91, 1.54)</td>
<td>7</td>
<td>7</td>
<td>13.16 (0.04)</td>
<td>54.4%</td>
</tr>
<tr>
<td>ICP management strategy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbiturate use</td>
<td>1.00 (0.77, 1.31)</td>
<td>4</td>
<td>556</td>
<td>5.75 (0.12)</td>
<td>47.8%</td>
</tr>
<tr>
<td>No barbiturate use</td>
<td>1.79 (1.27, 2.52)</td>
<td>4</td>
<td>225</td>
<td>0.69 (0.87)</td>
<td>0%</td>
</tr>
<tr>
<td>Trial duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–6 months</td>
<td>1.02 (0.79, 1.35)</td>
<td>5</td>
<td>546</td>
<td>7.00 (0.14)</td>
<td>42.9%</td>
</tr>
<tr>
<td>1–2 years</td>
<td>1.72 (1.24, 2.38)</td>
<td>3</td>
<td>234</td>
<td>0.29 (0.86)</td>
<td>0%</td>
</tr>
</tbody>
</table>

RR, relative risk; CI, confidence interval.
Another Possible Reason for Failed TBI Clinical Trials

- Targeting a single secondary injury mechanism may be inadequate to produce a discernable effect in clinical trials.

- Is it time to think about multiple treatment strategies?
What were the major findings from the 2008 NIH Combination Therapies for TBI workshop?

February, 2008

Rationale for combination therapies for TBI- may need to interrupt secondary injury at multiple points to achieve a significant clinical benefit
Combination Therapies for Traumatic Brain Injury: Prospective Considerations

Susan Margulies,1 Ramona Hicks,2 and The Combination Therapies for Traumatic Brain Injury Workshop Leaders*

Table 1. Initiation of Acute Secondary Events Post-TBI

<table>
<thead>
<tr>
<th>Within minutes(^a)</th>
<th>Minutes-24 h(^a)</th>
<th>24–72 h(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell/axon stretching, compaction of neurofilaments, impaired axonal transport, axonal swelling, axonal disconnection</td>
<td>Oxidative damage: Increased reactive oxygen and nitrogen species (lipid peroxidation, protein oxidation, peroxynitrite), reduction in endogenous antioxidants (e.g., glutathione)</td>
<td>Non-ischemic metabolic failure</td>
</tr>
<tr>
<td>Disruption of the blood brain barrier</td>
<td>Ischemia</td>
<td></td>
</tr>
<tr>
<td>Excessive neuronal activity: Glutamate release</td>
<td>Edema: Cytotoxic, vasogenic</td>
<td></td>
</tr>
<tr>
<td>Widespread changes in neurotransmitters:</td>
<td>Enzymatic activation: kallikrein-kinins, calpains, caspases, endonucleases, metalloproteinases</td>
<td></td>
</tr>
<tr>
<td>Catecholamines, serotonin, histamine, GABA, acetylcholine</td>
<td>Decreased ATP: Changes in brain metabolism (altered glucose utilization and switch to alternative fuels), elevated lactate</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage (heme, iron-mediated toxicity)</td>
<td>Cytoskeleton changes in cell somas and axons</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>Widespread changes in gene expression: cell cycle, metabolism, inflammation, receptors, channels and transporters, signal transduction, cytoskeleton, membrane proteins, neuropeptides, growth factors, and proteins involved in transcription/translation</td>
<td></td>
</tr>
<tr>
<td>Physiologic disturbances: Decreased cerebral blood flow, hypotension, hypoxemia, increased intracranial pressure, decreased cerebral perfusion pressure</td>
<td>Inflammation: Cytokines, chemokines, cell adhesion molecules, influx of leukocytes, activation of resident macrophages</td>
<td></td>
</tr>
<tr>
<td>Increased free radical production</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disruption of calcium homeostasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondrial disturbances</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Objectives of Combination Therapies Workshop

1. Identifying promising therapies

2. Challenges for testing combination therapies

3. Optimized strategies for developing single and combination therapies
Promising TBI Therapies- Interventions with Some Reasonable Amount of Preliminary Data Supporting Neuroprotective or Neurorestorative Efficacy

- **Citicholine** - membrane repair
- **Erythropoietin** - multiple neuroprotective and neurorestorative actions
- **Hypothermia** - inhibits many secondary injury mechanisms
- **Progesterone** – multiple neuroprotective actions
- **Cyclosporine A** - mitochondrial protection
- **Statins** – increased nitric oxide production ‡ improved CBF
- **Hypertonic saline** – improve CBF, reduce edema, etc.
Table 2. Study Design Considerations for Pre-Clinical TBI Single and Combination Therapy Development

- Was the candidate therapy evaluated in multiple models and in both rodent and gyrencephalic species?
- Was the dose–response effect evaluated over a clinically relevant time window?
- Did the studies include clinically relevant physiological monitoring?
- Were the studies blinded and randomized?
- Were the pharmacokinetics assessed in the target tissue of the experimental species and under conditions that reflect real-life clinical situations?
- Were surrogate markers evaluated to determine if the therapy attenuates the specific injury mechanisms that are being targeted?
- Were histological and functional outcome measures assessed following a prolonged survival interval to ensure that early treatment effects are not diminished?
- Was the candidate therapy evaluated in both genders, across the life-span, and across the spectrum of injury severities?
- Were the treatment effects replicated in several laboratories and/or observed in a multicenter pre-clinical consortium?
Summary of Recommendations

The workshop participants (listed below) agreed that the heterogeneity of TBI provides a strong rationale for the hypothesis that combination therapies will improve clinical outcomes compared to current single-agent interventions. Several steps were identified for moving research on combination therapies forward, including the following:

- Select therapies for use in combination that target multiple and complementary mechanisms of action.
- Validate surrogate markers to monitor treatment effects on brain injury and recovery for all stages of therapy development (in-vitro, animal, and human).
- Develop in-vitro, animal, and clinical platforms for coordinated studies across multiple laboratories.
- Use efficient designs for trials and data analysis.
- Be informed of the FDA regulations.
- Adopt a uniform standard of care for clinical trials, and mimic these standards in pre-clinical studies.
- Establish a shared database of positive and negative clinical and pre-clinical data.
**Example of Improved Efficacy of a Combination Therapy**

**Effect of Nimodipine + Tirilazad vs. Nimodipine Alone on 3 Month Outcome in Patients with Aneurysmal SAH**

(NF. Kassell et al. J. Neurosurg. 84:221-228, 1996)

<table>
<thead>
<tr>
<th>Nimo + Vehicle</th>
<th>Nimo + Tirilazad</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (accrued)</td>
<td>251</td>
<td>253</td>
</tr>
<tr>
<td>Good</td>
<td>53.0%</td>
<td>64.0%</td>
</tr>
<tr>
<td>Moderately disabled</td>
<td>13.5%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Severely disabled</td>
<td>9.6%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Vegetative survival</td>
<td>3.2%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Dead</td>
<td>21%</td>
<td>12%</td>
</tr>
<tr>
<td>Favorable outcome</td>
<td>67%</td>
<td>72%</td>
</tr>
<tr>
<td>Previous employment</td>
<td>52%</td>
<td>64%</td>
</tr>
</tbody>
</table>

![Figure 1: Severe vasospasm on day 7](image1)

![Figure 2: Severe vasospasm after rupture of a large right middle cerebral artery aneurysm.](image2)
What are the intrinsic differences in brain and spinal cord neuropathology that have implications for nutritional interventions following injury?
TBI or SCI

Petechial Hemorrhage

Iron Release

Depolarization

Voltage Dependent Channel Opening Na⁺, K⁺, Ca++

Glutamate Release

NMDA and AMPA Receptor Activation

Intracellular Ca²⁺ Overload

Mitochondrial Dysfunction

Energy Failure ↑Lactate

NOS Activation

Reactive Oxygen Formation (ONOO⁻)

AA Cascade Activation (COX1, COX2, 5-LO)

Calpain Activation

PGF₂α, TXA₂, LTs

Cytoskeletal Degradation

Oxidative Damage

Microvascular Damage

Ischemia

Neuronal Damage

Myelin Damage

Neurological Deficit
High Magnification of Immunohistochemical Staining of Oxidative Damage Markers

Brain parenchymal and microvascular nitrative and lipid peroxidative damage

Deng Y; Exp Neurol. 2007 May; 205(1):154-65
Role of Peroxynitrite in Acute Spinal Cord Injury Oxidative Damage

K.M. Carrico and E.D. Hall, J. Neurotrauma, 2009
Mitochondria from the uninjured spinal cord in comparison to brain display:

More LP products (4-HNE)  Compromised bioenergetics  Lesser potency of CsA protection
Tentative Conclusions Concerning Acute Treatment of TBI vs. SCI:

• Spinal cord displays increased oxidative stress and damage prior to and following injury compared to brain

• Spinal cord oxidative damage lasts longer than that seen in TBI models

• Same neuroprotective strategies should work in both TBI and SCI, but dose-response is likely to be shifted to the right and treatment may need to be more prolonged in the injured spinal cord
What are the leading anti-oxidation, anti-inflammatory therapeutics for TBI? How might these findings be applied to blast injuries?
• Microvascularly localized inhibitor of free radical-induced lipid peroxidation

• Efficacious in aneurysmal SAH

• Possibly efficacious in traumatic SAH

• High degree of safety
Peroxynitrite - Possibly the Key Reactive Oxygen (Nitrogen) Species in CNS Injury

- PG Synthase
- 5-Lipoxygenase
- Mitochondrial leak
- Xanthine oxidase
- Dopamine oxidation
- Neutrophils
- Macrophages
- Microglia

\[ \text{O}_2 \rightarrow \text{Nitric oxide synthase} \]

\[ \text{NO}^* \rightarrow \text{H}^+ \]

\[ \text{O}_2^- \rightarrow \text{ONOO}^- \rightarrow \text{ONOOh} \rightarrow \cdot \text{NO}_2 + \cdot \text{OH} \]

\[ [\text{O}=\text{N-O} \cdot \cdot \cdot \text{OH}] \]

\[ \text{SOD} \]

\[ \text{CO}_2 \]

\[ \text{ONOOCO}_2^- \rightarrow \cdot \text{NO}_2 + \text{CO}_3^- \cdot \]

\[ \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH} + \cdot \text{OH} \]

\[ \text{Catalase} \]

\[ \text{Fe}^{2+} \rightarrow \text{Hemoglobin} \]

\[ \text{Ferritin} \]

\[ \text{Transferrin} \]

\[ \text{O}_2 + \text{H}_2\text{O} \]
Lipid Peroxidation
LH → L· → LOO·

Protein Oxidation
Carbonyl formation

Protein Modification
Tyrosine nitration (3-NT; PN Biomarker)
Sulfhydryl oxidation (GSH Depletion)

PEROXYNITRITE-MEDIATED OXIDATIVE DAMAGE MECHANISMS IN ACUTE SCI

PEROXYNITRITE
Derived Radicals
(•NO₂, •OH, •CO₃)

DNA Damage
PARP activation ⇒ ↓ATP
The diagram illustrates the following processes:

1. **Injury** leads to **Ca**\(^{2+}\) influx, which is followed by **mitochondrial Ca**\(^{2+}\) uptake and **mtNOS activation**.

2. mtNOS activation results in the generation of **O\(_2^-\)** and **•NO**.

3. Mitochondrial ONOO\(^-\) leads to the formation of ONOOH and ONOO\(_2\)CO\(_2\) while generating **•OH, •NO\(_2, \)•CO\(_3\)**.

4. Tempol inhibits the formation of reactive oxygen species and reactive nitrogen species, preventing the downstream effects.

5. Tempol blocks **cell membrane oxidative damage**, **loss of Ca**\(^{2+}\) extrusion, **calcium overload**, and **calpain activation**.

6. Mitochondrial oxidative damage, mitochondrial dysfunction, and mitochondrial failure lead to **calcium release**.

7. Calcium release activates **calpain**, which induces **cytoskeletal degradation** and ultimately **neurodegeneration**.
Hall et al., J. Pharmacol. Exp. Ther. 1991

More potent and efficacious than tirilazad as an inhibitor of lipid peroxidation
Inhibitors of the Mitochondrial Permeability Transition Pore (mPTP)

Cyclosporin A

Methyl leucine

NIM811

Methyl isoleucine
Complete Inhibition of Mitochondrial Oxidative Damage by Cyclosporine A or NIM811

12hr 10 mg/kg NIM811 - 3-NT

12hr 10 mg/kg NIM811 - HNE

n = 6; **P<0.05 vs Sham; *p,0.05 vs Veh.

Review Article

Traumatic brain injury: an overview of pathobiology with emphasis on military populations

Iholja Cornak1 and Linda J. Noble-Haeusslein*

1National Security Technology Department, Johns Hopkins University Applied Physics Laboratory, Laurel, Maryland, USA and *Department of Neurological Surgery and Department of Physical Therapy and Rehabilitation Sciences, University of California, San Francisco, California, USA

Diagram:

BLAST

Local Response

Systemic Response

Cerebral Response

Mechanical Tissue Injury

Vascular Loading

ANS Activation

Perforation

Stretching

Shearing

Change in vascular tonus

Cardio-respiratory dysfunction

Activation of Neuro-Endocrine-Immune System

Initiation of secondary injury mechanisms

Hemorrhage

Synthesis/release of Autacoids

Hypoxia

Stress Response

Vago-Vagal Reflexes
<table>
<thead>
<tr>
<th>General features of TBI (Margulies and Hicks, 2009)</th>
<th>BINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse axonal injury</td>
<td>(Cemak et al, 2001a; Leung et al, 2008; Long et al, 2009a)</td>
</tr>
<tr>
<td>Degradation of the cytoskeleton</td>
<td>(Saljo et al, 2000)</td>
</tr>
<tr>
<td>Cortical and subcortical neuronal injury/death</td>
<td>(Kato et al, 2007; Moochhala et al, 2004)</td>
</tr>
<tr>
<td>Vascular-related changes (barrier breakdown, vasospasm, edema)</td>
<td>(Armonda et al, 2006; Cemak et al, 1996b)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>(Nakagawa et al, 2008)</td>
</tr>
<tr>
<td>Ischemia</td>
<td>NK</td>
</tr>
<tr>
<td>Glutamate excitotoxicity</td>
<td>NK</td>
</tr>
<tr>
<td>Changes in neurotransmitters</td>
<td>NK</td>
</tr>
<tr>
<td>Seizures</td>
<td>NK</td>
</tr>
<tr>
<td>Physiological disturbances</td>
<td>(Axelson et al, 2000; Bauman et al, 2009; Cemak et al, 1996b; Irwin et al, 1999)</td>
</tr>
<tr>
<td>Free radical generation</td>
<td>(Cemak et al, 2000, 2001b)</td>
</tr>
<tr>
<td>Disruption of calcium homeostasis</td>
<td>(Cemak et al, 1995)</td>
</tr>
<tr>
<td>Mitochondrial disturbances</td>
<td>NK</td>
</tr>
<tr>
<td>Metabolic disturbances</td>
<td>(Cemak et al, 1995)</td>
</tr>
<tr>
<td>Altered brain metabolism</td>
<td>(Cemak et al, 1996b)</td>
</tr>
<tr>
<td>Altered gene expression</td>
<td>(Saljo et al, 2002a, b)</td>
</tr>
</tbody>
</table>

Abbreviations: BINT, blast-induced neurotrauma; NK, not known; TBI, total-body irradiation.
Characterization of Plasma Magnesium Concentration and Oxidative Stress Following Graded Traumatic Brain Injury in Humans

IBOLJA CERNAK, VELJKO J. SAVIC, JELENA KOTUR, VERA PROKIC, MILIC VELJOVIC, and DRAGAN GRBOVIC
Military Medical Academy, Belgrade, Yugoslavia.

FIG. 7. Time-dependent alterations in plasma lipid peroxidation product malondialdehyde (MDA) concentration (mmol/L) in patients with indirect neurotrauma (INT), mild closed head injury (GCS 13–15), and extensive penetrating head injury (GCS 4–6) at various times postinjury. Control values (C) are presented as baseline. Bar = means ± SE. *p < 0.05, **p < 0.01, and ***p < 0.001 as compared to controls.
Blast-Induced (120 kPa) Neurotrauma in Rat Brain
R. Readnower and P. Sullivan, University of Kentucky
And R. McCarron, Naval Medical Research Center

Oxidative Damage

BBB Opening
What should we consider about findings on creatine and TBI? How might these findings be applied to blast injuries?
Dietary Supplement Creatine Protects against Traumatic Brain Injury

Patrick G. Sullivan, PhD,* Jonathan D. Geiger, PhD,† Mark P. Mattson, PhD,* and Stephen W. Scheff, PhD*
Creatine Supplementation:
- Maintains synaptosomal mitochondrial membrane potential (JC1)
- Reduces free radical formation (DCF)
- Decreases Ca\textsuperscript{++} accumulation (RHOD-2)
- Improves ATP levels

Creatine Supplementation:
- Increases mitochondrial Ca\textsuperscript{++} buffering capacity
In your opinion, what are nutrients/diets that have shown more promise and warrant further research regarding suppression of TBI injuries or recovery from TBI?
Promising Neuroprotective Nutraceuticals

- Small molecule scavengers-electron donors
  - Vitamin E (α-tocopherol)-principal peroxyl radical scavenger
  - Vitamin C (Ascorbic acid)-donates electron to vit. E radical
  - Glutathione (GSH)-LOO• scavenger
Lipid Peroxidative Depletion of Cat Spinal Cord Vitamin E After Compression Injury

Vitamin E concentration (μg/g wet wt ± S.E.)

- **Un-injured**: N=4
- **4 hr Post-injury**: N=11

**Vitamin E**

**Vitamin E Radical**

Hall et al., 1995
Lipid Peroxidation Also Plays a Role in Post-Traumatic Microvascular Damage as Shown by the Effect of Pretreatment With Vit. E + Se++ to Prevent the Decrease In White Matter SCBF

Data taken from Hall and Wolf, J. Neurosurg. 64:951, 1986
Vitamin E Pretreatment Enhances Recovery After Spinal Cord Compression Injury in Cats

D. Anderson et al., J. Neurotrauma 5:61, 1988
The effects of chronic two-fold dietary vitamin E supplementation on subarachnoid hemorrhage-induced brain hypoperfusion

Mark A. Travis and Edward D. Hall

CNS Diseases Research Unit, The Upjohn Company, Kalamazoo, MI 49001 (U.S.A.)

(Accepted 12 May 1987)

Comparison of intracranial pressure, mean arterial blood pressure, cerebral perfusion pressure, and cerebral vascular resistance following SAH in normal and vitamin E-supplemented animals

Vitamin E supplemented values represent mean ± S.E.M.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Pre-SAH</th>
<th>Time (min) after SAH</th>
<th>Change from pre-SAH 3 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>6</td>
<td>7.1 ± 1.6</td>
<td>12.5 ± 1.4</td>
<td>13.4 ± 2.4</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>6</td>
<td>1.9 ± 0.4</td>
<td>3.8 ± 2.0</td>
<td>4.3 ± 2.4</td>
</tr>
</tbody>
</table>
Vitamin E supplementation in diet for 4 weeks before injury

Valeria Conte,*†‡ Kunihiro Uryu,§ Scott Fujimoto,*† Yuemang Yao,¶ Joshua Rokach,** Luca Longhi,*†‡ John Q. Trojanowski,§ Virginia M-Y. Lee,§ Tracy K. McIntosh*† and Domenico Praticō¶

Vitamin E supplementation in diet for 4 weeks before injury
Naturally Occurring Lipid Peroxyl Radical Scavengers Shown to be Protective in TBI Experimental Models

Electron donation from phenolic hydroxyl (-OH)

Sources of other LOO• scavenging polyphenolic antioxidants
• blueberries
• strawberries
• spinach
• dark chocolate
• green tea