Metabolism, Neural Activation and Plasticity after TBI: A Developmental Perspective

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Summary

1. Introduction to Pediatric TBI
2. Metabolism and Metabolic Therapy
3. Neural Activation and Pro-plasticity Therapy
4. Effects of Repeated Injury in Development
5. Conclusions
Traumatic Brain Injury: Epidemiology

#1 cause of death and acquired disability in children and adolescents!!

CDC 2004 Report: TBI in the United States
Age of Injury and Mechanism

Mechanism of Injury varies by Age

*ANOVA, p < 0.0001

Valino H, Breault J, et.al. in preparation, 2012
Summary

1. Introduction to Pediatric TBI

2. Metabolism and Metabolic Therapy
   a) Neurometabolic Cascade
   b) Alternative Fuel Metabolic Therapy

3. Neural Activation and Pro-plasticity Therapy

4. Effects of Repeated Injury in Development

5. Conclusions
Neurometabolic Cascade of mTBI: Basic Pathophysiology

- Altered neurotransmission
- Ionic flux activation
- Cell Death
- Protease activation
- Energy Crisis
- Mitochondria (Mito)
- Axonal injury
- Glutamate
- Ca^{2+}
- K^+
- ADP
- ATP
- Pump

Altered neurotransmission
Post-TBI ketogenic diet reduces lesion volume in immature rats

Prins, et al., J Neurosci Res, 2005
Post-TBI transporter upregulation

TBI induces vascular endothelial expression of monocarboxylate transporter 2 (MCT2)

Prins & Giza, Dev Nsci 2006
Summary

1. Introduction to Pediatric TBI
2. Metabolism and Metabolic Therapy
3. Neural Activation and Pro-plasticity Therapy
   1. Impaired glutamatergic neurotransmission and experience-dependent plasticity
   2. Restoration of plasticity using glutamate agonist
4. Effects of Repeated Injury in Development
5. Conclusions
Traumatic Brain Injury: Fluid Percussion

Fluid percussion injury effects

- Diffuse concussive injury
- Dura intact
- Followed by apnea and unresponsiveness to toe pinch
- Normal open-field behavior as early as 1 day post-injury
- *Little, if any overt cell death in developing animals*
**Developmental TBI: NMDARs**

Protein levels of the NR2A subunit are selectively reduced after developmental TBI. NR1 & NR2B show little change.

Giza, Santa Maria & Hovda, J. Neurotrauma 2006

Li, et. al., National Neurotrauma Society abstract 2005

NR2A mediated postsynaptic currents are selectively reduced after developmental TBI.

Hippocampus: Ipsilateral NR2A

Hippocampus: Ipsilateral CA1
During a spatial working memory task, children post-acutely following moderate-severe TBI show much less network activation.

Imaging Post-TBI NMDAR Activation with phMRI: Rat

DCS administration selectively increases hippocampal rCBV. This activation is abolished 3-4 days after developmental TBI.

Santa Maria N.S., et al., J Neurotrauma abstr 2009
Experimental Design:

- **SHAM SURGERY**
  - STANDARD ENVIRONMENT
  - Enriched environment rearing for 17 days

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TBI Early in Life Results in a Loss of Developmental Potential

Morris water maze performance *improves* after enrichment, but *does NOT* improve with enrichment after developmental TBI.

*Giza, Griesbach and Hovda, Behav Brain Res 2005*
## What we have: FPI and NMDAR Summary

<table>
<thead>
<tr>
<th>Measure</th>
<th>P19 FPI</th>
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<tbody>
<tr>
<td>Molecular</td>
<td>NR2A (PID4)</td>
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<td>Phos/total CAMKII (PID4)</td>
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<td>Electro-physiological</td>
<td>Evoked EPSC (PID4)</td>
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<td>Behavioral (subacute)</td>
<td>NOR (PID4)</td>
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<td>Behavioral (chronic)</td>
<td>MWM Trials to Criterion (PID40)</td>
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<td>phMRI (subacute)</td>
<td>ΔrCBV (evoked) (PID3-5)</td>
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The concept of excitotoxicity led to the general idea that **GLUTAMATE WAS BAD** post-injury and should be blocked.

However, it is increasingly apparent that **GLUTAMATE CAN ALSO BE GOOD**.

*Ikonomidou & Turski, Lancet Neurol, 2002*
D-Cycloserine (DCS) Treatment Reverses TBI Dysfunction

D-cycloserine

- NMDAR co-agonist
- Binds at glycine site
- FDA approved agent (for TB)
- Good bioavailability
- Penetrates BBB

Treatment with DCS restores normal NR2A levels in rats

Santa Maria N.S., et al, J Neurotrauma abst 2007
Experimental Design:

Sham Surgery → Standard Environment → Enriched environment rearing for 17 days

Sham Surgery → Standard Environment → Enriched environment rearing for 17 days
D-Cycloserine (DCS) Treatment Restores post-TBI Plasticity

EE34 DCS effect on Sham groups

One-way ANOVA
* p<0.05
# p=0.19

EE34 DCS effect on LFP groups

Treatment with DCS has no effect in sham rats, but given after developmental TBI, DCS improves spatial memory in adulthood preferentially in EE reared animals

Santa Maria N.S., et al., J Neurotrauma abst 2008
What we have: FPI and NMDAR Summary

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<td>Molecular</td>
<td>NR2A (PID4) Phos/total CAMKII (PID4)</td>
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<td></td>
<td></td>
<td>Restored MWM Probe Trial (PID40-50)</td>
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<td>phMRI (subacute)</td>
<td>ΔrCBV (evoked) (PID3-5)</td>
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Future Clinical Directions

Can we use this... to turn this... into this... and will it then lead to...? ....this?
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Concussion in juvenile rat

APP staining at Post-injury day 1

Axonal injury and working memory impairment after repeat TBI can be modeled in rats.

Prins ML, et al., Dev Nsci 2010
Conclusions

1. The developing brain has both resiliencies and vulnerabilities to TBI.

2. The neurometabolic cascade of TBI is distinct in the young brain, and metabolic therapy with alternative substrates may be an age-specific treatment.

3. The young brain is resilient to TBI but shows altered / impaired neural activation and plasticity.

4. Judicious use of glutamate agonists coupled with behavioral interventions can restore experience-dependent plasticity after TBI.

5. Repeated injury in the young brain can result in worse sequelae, depending upon the timing of the injuries.
PROTECT ALL THE BRAINS!!!

Protected Brains

Unprotected Brain