May 8th, 10:30 AM - 12:00 PM

Rodent Traumatic Brain Injury as a Model for Human Traumatic Axonal Damage and Neurodegeneration

Nils Henninger
University of Massachusetts Medical School

Follow this and additional works at: https://escholarship.umassmed.edu/cts_retreat

Part of the Animal Diseases Commons, Nervous System Diseases Commons, Neurology Commons, Translational Medical Research Commons, and the Trauma Commons

Creative Commons Attribution-Noncommercial-Share Alike 3.0 License
This work is licensed under a Creative Commons Attribution-Noncommercial-Share Alike 3.0 License.
RODENT TRAUMATIC BRAIN INJURY AS A MODEL FOR HUMAN TRAUMATIC AXONAL DAMAGE AND NEURODEGENERATION

Nils Henninger, MD
Department of Neurology
-no disclosures-
OBJECTIVES

- Advantages and disadvantages of mouse trauma models
- Few examples of frequently used mouse models
- Similarities between mouse vs. human mild traumatic brain injury (TBI)
The Neuropathology and Neurobiology of Traumatic Brain Injury

Kaj Blennow,1,* John Hardy,2 and Henrik Zetterberg1,2
1Clinical Neurochemistry Laboratory, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Mölndal, SE-431 80 Mölndal, Sweden
2Department of Molecular Neuroscience and Reta Lilla Weston Laboratories, UCL Institute of Neurology, London WC1N 1PJ, UK
*Correspondence: kaj.blennow@neuro.gu.se
http://dx.doi.org/10.1016/j.neuron.2012.11.021

Figure 1. Molecular Pathophysiology of Concussion
A schematic flow chart of the molecular changes after rotational head injury that leads to concussion and knockout with loss of consciousness. Abbreviations: NMDA, N-methyl-D-aspartate.
Modeling mild TBI with axonal injury in mice is difficult because of their brain’s resilience to accelerational/rotational forces

**MOUSE BRAIN TRAUMA**

Disadvantages:
- Obvious differences related to developmental speed, brain size, gyration (surface area), gray-white matter ratio, specific compartmentalization, and complexity
- High resilience to angular acceleration injury (compact, small)

Advantages:
- Low cost and ethical concern compared to higher species
- Models key aspects of human brain injury
- Genetic versatility

http://www.visualphotos.com/image/2x3755739/close-up_of_a_human_foot_over_a_dead_mouse
**Mouse Brain Trauma Models (Examples)**

**Focal injury models:**
- Controlled cortical impact
- Head impaction

**Diffuse injury models:**
- Fluid percussion
- Blast injury models
- Closed head weight drop

?Mild
CCI causes traumatic axonal injury (TAI) at the expense of massive focal damage.

**CONTROLLED CORTICAL IMPACT (CCI)**

CCI delivers an impact onto the unprotected brain surface.

But, it requires a craniotomy and typically produces TAI in the vicinity of significant focal injury (*).
FPI produces TAI and avoids the focal injury but is tricky to perform

**FLUID PERCUSSION INJURY (FPI)**

FPI produces TAI uncomplicated by contusion, major inflammatory response, or significant astrocytic gliosis.

However, it requires an elaborate setup, craniotomy, and is prone to variability (worse with small brains).

**Figure 4** The initiator assembly of the MFP device. The initiator assembly consists of the fluid percussion pressure regulators and controls for triggering the device, and the Powerlab data acquisition system. The Powerlab system has additional outlets that could be connected to other devices for measurement of temperature and other physiological parameters, such as blood pressure and heart rate. Following injury, the pressure is recorded using the Chart4Windows 4.2 software program.
Closed head injury model is easy to perform, avoids craniotomy, and adaptable

**CLOSED HEAD TBI(CHI)**

CHI avoids a craniotomy and can be performed very quickly

CHI can easily be tailored to specific needs

- Weight 50 g
- Height 15 cm
- Impact area 3 mm
MILD CHI INDUCES TRANSIENT NEUROLOGICAL DEFICITS

PROTOCOL

TABLE 1 | Neurological severity score (NSS) for mice.

<table>
<thead>
<tr>
<th>Task</th>
<th>Description</th>
<th>Points (success/failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exit circle</td>
<td>Ability and initiative to exit a circle of 30 cm diameter within 3 min</td>
<td>0/1</td>
</tr>
<tr>
<td>Monoparesis/hemiparesis</td>
<td>Paresis of upper and/or lower limb of the contralateral side</td>
<td>0/1</td>
</tr>
<tr>
<td>Straight walk</td>
<td>Alertness, initiative and motor ability to walk straight</td>
<td>0/1</td>
</tr>
<tr>
<td>Startle reflex</td>
<td>Innate reflex; the mouse will bounce in response to a loud hand clap</td>
<td>0/1</td>
</tr>
<tr>
<td>Seeking behavior</td>
<td>Physiological behavior as a sign of &quot;interest&quot; in the environment</td>
<td>0/1</td>
</tr>
<tr>
<td>Beam balancing</td>
<td>Ability to balance on a beam of 7 mm width for at least 10 s</td>
<td>0/1</td>
</tr>
<tr>
<td>Round stick balancing</td>
<td>Ability to balance on a round stick of 5 mm diameter for at least 10 s</td>
<td>0/1</td>
</tr>
<tr>
<td>Beam walk: 3 cm</td>
<td>Ability to cross a 30-cm long beam of 3 cm width</td>
<td>0/1</td>
</tr>
<tr>
<td>Beam walk: 2 cm</td>
<td>Same task, increased difficulty on a 2-cm wide beam</td>
<td>0/1</td>
</tr>
<tr>
<td>Beam walk: 1 cm</td>
<td>Same task, increased difficulty on a 1-cm wide beam</td>
<td>0/1</td>
</tr>
<tr>
<td>Maximal score</td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

NSS 0-10 points

Neurological Severity Score

3-cm falling height

2-cm falling height

Time after trauma

NSS
LASER DOPPLER FLOWMETRY INDICATES TRANSIENT POSTRAUMATIC HYPOPERFUSION

Pediatric Sp
Todd A. M
Pediatr

Alterations
J M. Cecil
2011;

Impact

<table>
<thead>
<tr>
<th>Time from Impact</th>
<th>rCBF (% baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>100</td>
</tr>
<tr>
<td>1 min</td>
<td>70</td>
</tr>
<tr>
<td>5 min</td>
<td>60</td>
</tr>
<tr>
<td>10 min</td>
<td>50</td>
</tr>
<tr>
<td>15 min</td>
<td>40</td>
</tr>
<tr>
<td>20 min</td>
<td>30</td>
</tr>
<tr>
<td>30 min</td>
<td>20</td>
</tr>
<tr>
<td>40 min</td>
<td>10</td>
</tr>
<tr>
<td>50 min</td>
<td>10</td>
</tr>
<tr>
<td>60 min</td>
<td>10</td>
</tr>
<tr>
<td>70 min</td>
<td>10</td>
</tr>
<tr>
<td>80 min</td>
<td>10</td>
</tr>
<tr>
<td>90 min</td>
<td>10</td>
</tr>
</tbody>
</table>

- Ipsilesional LDF signal (n=8)
- Contralesional LDF signal (n=2)

Notes:
- Participants who completed only 2 study visits.
- This value was eliminated from the mean calculation as this participant was an extreme outlier: see discussion section.
BETA AMYLOID PRECURSOR PROTEIN (bAPP)-STAINING MARKS TRAUMATIC AXONAL INJURY

Johnson et al., ExpNeurol 2012
Post-traumatic bAPP-positive neurons are predominantly found in the right hemisphere CA3 and cortex.
SUMMARY AND OUTLOOK

- Mouse closed head TBI mimics several important aspects of human concussion injury:
  - Transient neurological deficits (particularly balance)
  - Posttraumatic hypoperfusion
  - Traumatic axonal injury
  - Neuronal stress and degeneration
- Further detailed histological evaluation
- Impact on cognitive measures
- Evaluating axonal death pathways
- Testing of novel therapeutic strategies to mitigate axonal/neuronal traumatic injury