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

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RODENT TRAUMATIC BRAIN INJURY AS A MODEL FOR HUMAN TRAUMATIC AXONAL DAMAGE AND NEURODEGENERATION

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-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

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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
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 (*).
**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).
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
**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 ‘interest’ 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>

**Neurological Severity Score**

NSS 0-10 points
Laser Doppler Flowmetry Indicates Transient Posttraumatic Hypoperfusion

Pediatric Sp
Todd A. M
Pediatr

Alterations
M. Cecil
2011;

Impact

Time from Impact

Baseline 1 min 5 min 10 min 15 min 20 min 30 min 40 min 50 min 60 min 70 min 80 min 90 min

rCBF (% baseline)

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

a Participants who completed only 2 study visits.
b 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

Ann C. McK
Brandon I

McKee et al

TABLE 5. Micro

Case:

1
2
3
4
48
A*
B*
C*

C. Degenerative neurons
tests (B.) and neurodegeneration (C.) as shown by

0 1 2 3 4

bAPP/Nissl staining

Left Cortex (20x)

Right CA3 (20x)

Right Cortex (20x)

Right CA3 (60x)

Right Cortex (60x)

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