Stressed by Sleep Disruption after Traumatic Brain Injury

Olga N. Kokiko-Cochran, PhD
Assistant Professor
Department of Neuroscience

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER
TRAUMATIC BRAIN INJURY

ALZHEIMER’S DISEASE
TBI and AD-like Pathology

- Beta-amyloid (Aβ)
- Reactive Microglia
- Neurofibrillary Tangles (NFT)

Johnson et al., 2012; Johnson et al., 2013
Hypothesis: Post-injury neuroinflammation is critical in mediating outcome following TBI
Neuroinflammatory Response to TBI is *Dynamic*

- Microglia / Macrophage Related Neuroinflammation
- Time
- Normal Health Burden

- Post-TBI immune challenge
- Repetitive TBI
- Pre-TBI immune challenge
- Single TBI

Kokiko-Cochran & Godbout, 2018
Hypothesis: Post-injury neuroinflammation is critical in mediating outcome following TBI

Neuroinflammatory response is modulated by previous, coincident, and subsequent immune challenge
Are there other post-injury stressors that influence the inflammatory response to TBI?
External Stressors for People

Sleep Disturbances
External Stressors for Mice

Restraint Stress  Tail Suspension  Forced Swim

Sleep Disturbances

Tapp et al., 2019
Sleep Disruption is Associated with...

- Decreased performance and alertness
- Memory and cognitive impairment
- Increased stress
- Poor quality of life
- Occupational injury
- Automobile injury
- High blood pressure
- Heart attack
- Heart failure
- Stroke
- Obesity
- Psychiatric problems
Changing Behaviors Associated with Alzheimer’s Disease (AD)

- Cognitive
- Agitation
- Apathy
- Inappropriate Sexual Behavior
- Sleep Disturbances
Hypothesis

Sleep disruption is a physiologically relevant stressor that exacerbates neuroinflammation and compromises recovery after TBI
### Experimental Methods

#### 8-Month Old C57BL/6 Male & Female

<table>
<thead>
<tr>
<th>Condition</th>
<th>Human</th>
<th>Rat</th>
<th>Mouse</th>
<th>Cat</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary diurnal sleep phase</td>
<td>Dark</td>
<td>Light</td>
<td>Light</td>
<td>Dark</td>
<td>Dark</td>
</tr>
<tr>
<td>Sleep pattern</td>
<td>Monophasic or diphasic</td>
<td>Polyphasic</td>
<td>Polyphasic</td>
<td>Polyphasic</td>
<td>Polyphasic</td>
</tr>
<tr>
<td>Daily sleep duration</td>
<td>7-8 h</td>
<td>12-15 h</td>
<td>12-15 h</td>
<td>12-13 h</td>
<td>9-14 h</td>
</tr>
<tr>
<td>Length of sleep bouts</td>
<td>6-8 h</td>
<td>10-14 min</td>
<td>2-4 min</td>
<td>78 min</td>
<td>45 min</td>
</tr>
</tbody>
</table>

- **Left Hemisphere Contralateral**
- **Right Hemisphere Ipsilateral**

**7-11 AM Daily**

**Why?**
Experimental Timeline

DPI = days post-injury
Implantable Telemetry Allows EEG/EMG Recording in Freely Moving Mice
Week 1 Preliminary Data – Hourly Average Over 7 Days

% Time in REMS

Zeitgeber (Hours)

SF

Sham CON  Sham SF  TBI CON  TBI SF

n = 1-2/group
TBI SF Mice Display Deficits in Spatial Working Memory 7 DPI

DPI = days post-injury
TBI Increases Cortical Microglia Reactivity 7 DPI

DPI = days post-injury
SF Results in Unique Cortical Gene Expression in Sham and TBI Mice 7 DPI

DPI = days post-injury
Hippocampus Intersects TBI and Stress

[Diagram showing the interaction between hippocampus and stress pathways]

Corticosterone concentration (µg/dl)

Time (h)

0 8 16 24

0 25 50 75

CRH

Pituitary

ACTH

Adrenal

Peripheral organs

Hippocampus

CA1

CA3

DG

PVN

DR

TRENDS in Pharmacological Sciences

Joels 2006
Post-TBI SF Disrupts Neuronal Activity in CA1 and CA3 30 DPI

DPI = days post-injury
Dysregulated Neuronal Activity after SF Extends to the BNST and PVN 30 DPI

BNST = bed nucleus of the stria terminalis
PVN = paraventricular nucleus
DPI = days post-injury
Response to SF is Uniquely Influenced by TBI Through 30 DPI
Spatial Reference Memory is Intact Following 30 Days of Recovery
Hypothesis

Sleep disruption is a physiologically relevant stressor that exacerbates neuroinflammation and compromises recovery after TBI
Available to Address Questions Related to:

- **Experimental models of TBI and AD**
- **Relationship between TBI and AD**
- **Stress-immune communication**
- **Sleep disruption as a stressor**
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@KokiCoLab
www.kokikocochranlab.com