Animal models of postoperative delirium research

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October 24, 2014 (Boston)

Why do we need the animal model to study postoperative delirium?

- Mechanistic hypothesis testing:
  - Interaction of Aβ/Tau and neuroinflammation.
- Vulnerable window assessment:
  - Age dependent?
- Are there less provocative anesthetic:
  - Isoflurane versus desflurane.
- Potential treatment and prevention:
  - Anti-Aβ, anti-Tau and anti-inflammation.

Animal studies of delirium

- There are few animal models available to study delirium at the present time.
- It is important to establish animal models of delirium.
- We then can determine whether the perioperative factors (e.g., anesthesia, surgery, pain, and sleep deprivation, which could contribute to POCD) can also contribute to the postoperative delirium.

T-maze alternation: working memory

Dr. Colm Cunningham

- Mice will escape from shallow water.
- It needs training period (10 trails).
- It assesses working memory in rodents.

(Murray et al., Neurobiology of Aging, 2012)
Animal studies of delirium

- We have set out to observe several animal nature behaviors following the treatment of scopolamine and following the abdominal surgery under isoflurane anesthesia.

- The ultimate goal is to develop a method of ”CAM in mice”

“Cam in mice”

- Acute onset and fluctuating course:
  - Timecourse studies.

- Inattention
  - Attention deficit assessment.

- Disorganized thinking
  - Freezing behavior and others.

- Altered level of consciousness
  - Open field test and others.

Nature behavioral observation

- Attention level (Millecamp et al., 2004).

- Freezing episodes.

- Open field tests.

- Timecourse investigation.

Attention level

\[ \text{Attention level} = \frac{\text{Duration of the new object exploration}}{\text{Total duration of all cumulated objects exploration (i.e. 3 familiar + the new one)}} \times 100 \]

(Millecamps et al., 2004)

Freezing episodes

- Definition: No movement except respiration.

- Detected and analyzed by Any-Maze (Stoelting, Wood Dale, IL).
**Open field test**

- Definition: The time spent in the zone near the wall during the open field test.
- Detected and analyzed by Any-Maze (Stoelting, Wood Dale, IL).

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**Scopolamine in mice**

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**Anesthesia and surgery in mice**
Effects of Anesthesia and Surgery on mice “CAM”

<table>
<thead>
<tr>
<th>Scopolamine</th>
<th>Anesthesia &amp; Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-8-month mice</td>
<td>18-month mice</td>
</tr>
<tr>
<td>30 min</td>
<td>12h</td>
</tr>
<tr>
<td>Near the wall</td>
<td>↑</td>
</tr>
<tr>
<td>Attention level</td>
<td>↓</td>
</tr>
<tr>
<td>Freezing episode</td>
<td>↓</td>
</tr>
</tbody>
</table>

*↑ and ↓ indicate significant increase (P < 0.05) and decrease (P <0.05) compared with saline or sham group at the same time point, respectively.

Animal models of perioperative factors

Animal: Rats.
Anesthesia: 1.2% isoflurane, 70% nitrous oxide, and 30% oxygen for two hours.
Cognitive function determination: 12-arm radial maze.

(Culley et al., Anesthesiology, 2004)

General anesthesia

Animal: Mice.
Anesthesia: Halothane (0.8–1%) or isoflurane (0.9–1%) in 30% oxygen, balanced by N2 for two hours.
Cognitive function determination: Morris Water Maze.

(Bianchi et al., Neurobiology of Aging, 2008)
Animal: Mice.
Anesthesia: 1.4% isoflurane for two hours.
Cognitive function determination: Fear conditioning system.

(Fianchi et al., Neurobiology of Aging, 2008)
(Zhang et al., Annals of Neurology, 2012)
**Animal:** Rats.

**Surgery:** Splenectomy.

**Anesthesia:** Fentanyl and droperidol (i.p.).

**Cognitive function determination:** Y-Maze.

(Wan et al., Anesthesiology, 2007)

**Animal:** Mice.

**Surgery:** Hepatectomy.

**Anesthesia:** Chlora hydrate (i.p.).

**Cognitive function determination:** Morris Water Maze.

(Wan et al., Critical Care Medicine, 2010)

**Animal:** Mice.

**Surgery:** Incisional or chemical pain.

**Anesthesia:** local injection of bupivacaine.

**Analgiesia:** EMLA (local anesthetics).

**Cognitive function determination:** Fear conditioning system and Morris Water Maze.

(Zhang et al., Journal of Neuroscience, 2013)

(Terrando et al., PNAS, 2010)

**Surgery plus local anesthesia**

**Animal:** Mice.

**Surgery:** Opening and closing abdomen.

**Anesthesia:** local injection of bupivacaine.

**Analgesia:** EMLA (local anesthetics).

**Cognitive function determination:** Fear conditioning system.

(Xu et al., Scientific Reports, 2014)

(Xu et al., PLoS One, 2014)

**Pain**

**Animal:** Mice.

**Surgery:** Incisional or chemical pain.

**Cognitive function determination:** Fear conditioning system.

(Yang et al., Anesthesia and Analgesia, 2014)
Sleep deprivation

Animal: Mice.

No sleep for 24 hours.

Cognitive function determination: Fear conditioning system.

(Zhu et al., Neurobiology of Disease, 2012)

Summary and Conclusion

- The employment of several animal models has suggested that perioperative factors, e.g., anesthesia, surgery, pain and sleep deprivation, may contribute to the cognitive impairment in rodents.

- Whether these perioperative factors can contribute to postoperative delirium remains largely to be investigated.

- Thus, it is important to establish animal models of postoperative delirium.

Acknowledgements

Current:
Yuanlin Dong
Yijing (Laura) Zhang
Long Fan
Fang Fang
Lining Huang
Cheng Li
Wankun Chen
Gulyun Cui
Xiaomin Xu
Guangyi Zhao
Jeffery Zimering
Lauren Schroeder
Arther Wang
Celeste Swain

Collaborators:
Harvard:
Rudolph E. Tanzi
Gregory Crosby
Deborah Culley
Edward Marcantonio
Keith Johnson

Capital Medical University, Beijing:
Tianzuo Li
Yun Yue
Ming Tian

Tongji University, Shanghai:
Yuan Shen

Supports:
NIH R01 GM088801
NIH R01 AG041274
Investigator-Initiated Research Grant from Alzheimer’s Association

Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital