The Influence of Orexin Antagonist, SB-334867, on Cognitive Flexibility

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Alzheimer’s Disease

ALZHEIMER’S DISEASE IS THE 6TH LEADING CAUSE OF DEATH IN THE UNITED STATES

MORE THAN 5 MILLION AMERICANS ARE LIVING WITH ALZHEIMER’S BY 2050, THIS NUMBER COULD RISE AS HIGH AS 16 MILLION

MORE THAN 15 MILLION AMERICANS provide unpaid care for people with Alzheimer’s or other dementias

IN 2016 these caregivers provided an estimated 18.2 BILLION HOURS of care valued at over $230 BILLION

EVERY 66 SECONDS someone in the United States develops the disease

35% of caregivers for people with Alzheimer’s or another dementia report that their health has gotten worse due to care responsibilities, compared to 19% of caregivers for older people without dementia

1 IN 3 seniors dies with Alzheimer’s or another dementia

IT KILLS MORE THAN breast cancer and prostate cancer COMBINED

In 2017, Alzheimer’s and other dementias will cost the nation $259 billion. By 2050, these costs could rise as high as $1.1 TRILLION

Since 2000, deaths from heart disease have decreased by 14% while deaths from Alzheimer’s disease have increased by 89%
Cognitive Flexibility

The ability for one to adapt to ever-changing situations, which normally has been seen to decline with age. (Brown & Tait, 2016)

Measures of cognitive flexibility:

*Human Model*
- The Wisconsin Card Sorting Task (Grant & Berg, 1948)
Cognitive Flexibility

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Measures of cognitive flexibility:

*Rodent Model*

- Set Shift Task (Arnold et al., 2002; Brady & Floresco, 2015; Cabrera et al., 2006)
Acetylcholine transmission to the hippocampus and neocortex from the basal forebrain is disrupted following degeneration of cholinergic neurons. (Bigl, Woolf, & Butcher, 1982)
The Orexins

- Class of neuropeptide (Sakurai et al., 1998)
- Involved in feeding and sleep (Sakurai et al., 1998; Smart & Jerman, 2002)
- Receptors located in the Basal Forebrain (Liu et al., 2015; Marcus et al., 2001)
- Modulator of ACh (Fadel et al., 2005)

Figure derived from Peyron et al. (1998)
Putting it all together

Next Steps

Orexin

Orexin & ACh

ACh & the Basal Forebrain

Attention, Learning & Memory

The Cholinergic Hypothesis

- Olfactory reversal discrimination task
- Reversal of rule
  - Trials to criteria
    - Antagonist > control
## Hypotheses

<table>
<thead>
<tr>
<th>Rule</th>
<th>Prediction</th>
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<tbody>
<tr>
<td>$h_1$ Trials to Set</td>
<td>Control = Antagonist</td>
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<tr>
<td></td>
<td>Trials to Shift</td>
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<tr>
<td>$h_2$ Errors to Set</td>
<td>Control = Antagonist</td>
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Methods: Subjects

- 9 male Sprague-Dawley rats
- 56 PND upon arrival

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<td>n = 3</td>
<td>n = 6</td>
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Methods: Pretraining

Phase 1
- FR-1 schedule of reinforcement
- Both levers extended
- House light + cue lights illuminated
- Criteria: 50 consecutive presses 2 days in a row

Phase 2
- FR-1 schedule of reinforcement
- Light cue + lever extension paired, alternating sides
- Criteria: ≥ 5 omissions 2 days in a row

Side Bias
- Both levers extended
- Side preference by left or right lever pressed first most often
Methods: Cannulation

- Stereotaxic surgery
  - nbM bilateral guide cannula
  - Coordinates
    - AP = -0.92 mm
    - M/L = ±3.8 mm
    - DV = -0.92 mm
Methods: Set

Rule: Always press LEFT lever
Ignore visual cue

Figure reproduced with permission
(Brady & Floresco, 2015)
Methods: Infusion

control
aCSF

Orexin antagonist: SB-334867

n = 3
n = 6
Methods: Shift

Rule: Always press lever with CUE light above it

Figure reproduced with permission (Brady & Floresco, 2015)
Results: Trials to Criteria

• No significant main effects
  • time
    \( F(1,7) = .480, p = .511, \eta^2 = .084 \)
  • drug
    \( F(1,7) = .300, p = .601, \eta^2 = .041 \)

• No group x time interaction
  \( F(1,7) = .148, p = .712, \eta^2 = .021 \)

• Between-group difference during shift not significant,
  \( t(7) = .640, p > .05, \eta^2 = .055 \)
Results: Errors to Criteria

- No significant main effects
  - time
    \[ F(1,7) = .660, \ p = .443, \ \eta^2 = .086 \]
  - drug
    \[ F(1,7) = .216, \ p = .656, \ \eta^2 = .030 \]

- No group x time interaction
  \[ F(1,7) = .220, \ p = .653, \ \eta^2 = .030 \]
Results: Types of Errors

• No significant main effect
  • error type
    $F(1,7) = 1.401, \ p = .275, \ \eta^2 = .167$
  • drug
    $F(1,7) = .116, \ p = .744, \ \eta^2 = .016$

• No group x error type interaction
  $F(1,7) = .497, \ p = .504, \ \eta^2 = .066$

• Control rats made less perservative errors than antagonist group
Results: Histology

Bregma: -0.92 mm

Image derived from http://www.brainmaps.org
Discussion: SB-334867 and Performance

- No group differences were found

- Trends in performance align with hypotheses
  - Trials to Shift: Control < Antagonist
  - Errors to Shift: Control < Antagonist
    ▪ Antagonist group made more perseverative errors

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Discussion: Implications

▪ Patterns in performance (and errors) mimics that of previous research
  – Piantadosi et al. (2015)
  – Cabrera et al. (2006)

▪ Patterns in performance (and errors) mimics the reversal of previous research
  – Fadel et al. (2005)
  – Zajo et al. (2016)

▪ ACh is implicated in cognitively-demanding tasks (Arnold et al., 2002)

▪ ACh is likely transmitted through the BFCS during performance of operant control tasks (Arnold et al., 2002)
Discussion: Limitations

- Inadequate sample size
- Histology
- Did not perform microdialysis
- Administration of a limited dose of SB-334867 only
Discussion: Future Directions

▪ More subjects!
▪ Comparison to administration of OxA agonist
▪ Microdialysis
▪ Different doses of SB-334867
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References


