Opening the Therapeutic Window for Estrogen Treatment through Hippocampal ER-alpha Overexpression

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Therapeutic Window

- Average age for the onset of menopause is 51 year of age
- Estrogen therapy promotes cognitive function if treatment is initiated around the time of onset
- Treatments initiated at ages 65 and over have no effect

What is regulating this therapeutic window?
Estrogen Receptors

- Estrogen receptors: alpha (ERα) and beta (ERβ)
- Estrogen receptor levels decline with age in the hippocampus

(Shughrue 1997, Mehra, 2005)
Experimental Design

Fischer 344 female rats
* AAV1 for ERα, ERβ or GFP
^ Estrogen benzoate (EB) or oil treatment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td>GFP+EB</td>
<td>n=13</td>
<td></td>
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<tr>
<td>GFP+Oil</td>
<td>n=12</td>
<td></td>
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<tr>
<td>ERβ+EB</td>
<td>n=11</td>
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15 weeks without estrogen

OVX
Pretest SWM
* AAV1 Injections
Final SWM

Sacrificed 48 hrs. after final EB treatment
Efficacy of AAV1

- CA1 region of hippocampus
- ~2800 µm anterior/posterior
- Expression in NeuN+ neurons
Spatial Training

![Graph showing distance (cm) vs. training blocks for different groups: ERα, EB and Oil (red circles), ERβ, EB and Oil (blue triangles), and GFP, EB and Oil (green squares). The graph indicates a decrease in distance as training blocks increase, with significant differences marked by asterisks (*) at specific blocks.](chart.png)
Spatial Water Maze – Probe Trials

Acquisition – No Delay

Retention – 1 hour Delay

Relearning – No Delay

**Discrimination Index**

- **Oil**
- **EB**

**Spatial Water Maze – Probe Trials**

- **GFP**
- **ERβ**
- **ERα**

**Acquisition – No Delay**

- **p = 0.051**
- **p < 0.05**

**Retention – 1 hour Delay**

- **p < 0.05**

**Relearning – No Delay**
Synaptic Response

Stimulation Strength (V)

Total fEPSP Slope (mV/ms)

NMDAR fEPSP Slope (mV/ms)

- GFP+Oil, n=4/8 animals/slices
- GFP+EB, n=4/8 animals/slices
- ERα+Oil, n=4/8 animals/slices
- ERα+EB, n=5/10 animals/slices

* denotes significant differences.
Conclusion

- Timeframe of experiment is outside of the therapeutic window (EB treatment had no effect on GFP control animals)
- Increasing expression of ERα
  - restored the beneficial effects of E2 therapy on hippocampal-dependent spatial memory
  - increased the NMDAR-mediated synaptic responses
- Use this information to design healthier pharmacological choices for aging women
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