INTRODUCTION

Women undergo cognitive changes as a result of menopause and aging (Halbreich et al., 1995). Age-related cognitive changes involve cholinergic function/dysfunction (Dumas and Newhouse, 2011). Estrogen effects on cognitive processes after menopause are mediated partially through salutary effects on brain cholinergic systems (Dumas et al., 2006). Estrogen effects on brain cholinergic system-mediated cognitive performance are age-dependent (“critical window hypothesis”) (Dumas and Newhouse, 2008). Estrogen affects age-related changes in brain cortical activity (Dumas et al., 2010) and can reverse anti-cholinergic drug effects on task-related brain activity (Dumas, Newhouse et al., 2011).

However, estrogen treatment begun after menopause is not ideal due to risks associated with long-term use, thus there is a search for new agents that will stimulate estrogen receptors to improve cognition in late life (Brinton 2002).

RESEARCH QUESTION

Can tamoxifen produce positive effects on cholinergic-related cognition in postmenopausal women?

METHODS

Demographics:

- 21 cognitively normal women, ages 50-74

<table>
<thead>
<tr>
<th>BMI</th>
<th>Mean Age (y) (50-74)</th>
<th>Education (y)</th>
<th>Years Since Menopause</th>
<th>Length of Prior HT Use (11/21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.7 (4.8)</td>
<td>60.8 (7.5)</td>
<td>15.8 (2.1)</td>
<td>13 (11.9)</td>
<td>2 wks-10.5 yrs</td>
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APOE genotyping showed the following breakdown: APOE ε2/2 = 0; APOE ε2/3 = 1; APOE ε2/4 = 1; APOE ε3/3 = 11; APOE ε4/3 = 7; APOE ε4/4 = 0.

Pharmacological Challenge:

After both 3 month treatments of TMX or placebo, subjects completed a 5 drug challenge days throughout a time span of 2 weeks, at least 48 hours apart. For each participant, the drug sequence was randomized. Drugs administered during challenge days were:

- Scopolamine (SCOP) is a muscarinic cholinergic antagonist that was intravenously administered at a dose of 2.5µg/kg and 5.0µg/kg body weight.
- Mecamylamine (MECA) is a nicotinic cholinergic antagonist with oral doses of 0 mg and 20 mg.

Matching placebos

RESULTS

Selective Reminding Task: TMX Improves Verbal Recall after Cholinergic Antagonist

![Graph showing TMX Main Effect](image)

- TMX delays verbal recall compared to placebo

Virtual Morris Watermaze (Spatial Navigation): TMX Improves Performance after Cholinergic Antagonist

![Graph showing Platform Latency across blocks after MECA](image)

- TMX treatment improves spatial memory

DISCUSSION

- These data show that TMX treatment improved verbal episodic memory and spatial navigation after cholinergic blockade.
- TMX appears to act as an estrogen-like agent to enhance brain cholinergic system activity and improve cognitive performance that involves hippocampal functioning.
- TMX effects may be particularly positive in APOE+ individuals, suggesting gene-specific effects.
- SERMs such as TMX may have long-term benefits on brain function without some of the liabilities of estradiol.
- TMX or other SERMs can be considered for prevention or treatment of cognitive changes in aging (Newhouse et al., 2013).

REFERENCES


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