Combined Effects of Estradiol & Cortisol on Cognition

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Basic science literature continues to support numerous neuroprotective actions of estrogen (estradiol)

- Actions that should theoretically protect against the development of Alzheimer’s disease by
  - increasing neurotransmission & CBF
  - modulating various growth proteins
  - ameliorating of beta-amyloid neurotoxicity

However, the benefits of estradiol for postmenopausal women are not consistently reported in clinical studies

- Disparate results may relate to a number of factors
  - timing of HRT relative to menopause
  - type of estrogen administered & estradiol levels achieved
  - co-administration with a progestin
Gonadal hormones influence reactivity of the hypothalamic-pituitary-adrenal axis to stress (Lund et al. 2004; Shors 2006; Bowman et al. 2002)

- Stressed-induced impairments on cognition are ameliorated by estradiol administration in animal studies (Bowman et al. 2002)

- Stress-induced hormonal response is exacerbated for estradiol-treated animals (Lund et al. 2004; Burgess & Handa 1992)
Elevated cortisol is linked to impaired declarative memory, & impaired executive function (Li et al., 2005; Birnbaum 2004)

Increased HPA axis activity may contribute to neurodegeneration & AD pathology in particular (Peskind, Wilkinson, Petrie, Schellenberg, Raskind, 2001)
Cortisol ... *PLUS* Estradiol

- Acute stress & elevated cortisol IMPROVES associative learning in male rats but IMPAIRS performance in female rats (Shors et al. 1998; Wood et al. 2001)

- Sex differences in rat hippocampal spine density formation & opposite stress-induced consequences (Shors et al. 2004)

- Estradiol-treated ovariectomized rats vs. controls have lingering HPA axis sensitivity after a period of repeated stress (Lunga & Herbert, 2004)

- Cortisol levels climb with age (van Cauter et al. 1996; Laughlin & Barrett-Connor, 2000); and in response to a cognitive challenge, levels rise MORE for older women than for older men (Seeman et al. 2001)
To examine whether increased cortisol mediates cognitive response to estradiol for healthy postmenopausal women

To examine the independent & combined effects of estradiol & cortisol on insulin-like growth factor (IGF) activity; an important growth factor not only for aging in general, but also for aging cognition

To examine the influence of estradiol+cortisol on a peptide linked to the development of Alzheimer’s disease
EsCort Study: Hypotheses

- Estradiol administration will have a beneficial effect on cognition
- Elevated cortisol will detrimentally affect cognitive performance
- Combined estradiol + cortisol administration will
  - attenuate estrogen-induced cognitive benefits
  - but ... ameliorate cortisol-induced impairments
Study Design

2 Weeks

Medical Screening for Eligibility & Practice Cog Tests

Baseline Visit

Week 8 Visit

Week 4 Visit

Cortisol (90 mg/d) or Placebo pills for 4 days

Estradiol (0.10 mg/d) or Placebo skin patch

Blood Cog Tests

Blood Cog Tests

Blood Cog Tests
Cognitive Tests

- Executive Function
  - Stroop Color-Word Interference Test
  - Self-ordered Pointing Test (SOPT)
- Declarative Memory
  - Story Recall
  - Hopkins Verbal Learning Test
  - Delayed Match-to-Sample
  - Verbal Fluency

Blood Assays

- Cortisol (total, free, cbg)
- Estradiol
- IGF (total IGF-1, free IGF-1, IGFBP-3)
- $\beta_40$, $\beta_42$

Increased IGF linked to reduced $\beta$ clearance

 Estradiol lowers & cortisol raises IGF-1
## Subjects

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<th>Cortisol Only</th>
<th>Estradiol Only</th>
<th>Estradiol +Cortisol</th>
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<tr>
<td><strong>N</strong></td>
<td>10</td>
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<td>9</td>
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<tr>
<td><strong>Mean Age (sd)</strong></td>
<td>70 (8)</td>
<td>72 (8)</td>
<td>74 (9)</td>
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<td><strong>Mean DRS (sd)</strong></td>
<td>139 (2)</td>
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<td><strong>Mean BMI (sd)</strong></td>
<td>28 (3)</td>
<td>29 (8)</td>
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Results

A. Estradiol

B. Cortisol
Cognitive Effects
# Stroop Color-Word Interference

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Stroop Color-Word Interference
~ Computer Administration ~

Color Naming

Voice-onset Latency (ms)

match vs mismatch

BLUE (match)

RED (mismatch)
Name the Ink Color
BLUE
Name the Ink Color
Stroop Color-Word Interference

Color Naming : Change from Baseline

![Graph showing the effect of different treatments on interference scores. The x-axis represents different conditions: Placebo, Estradiol Alone, Estradiol + Cortisol, and Cortisol Alone. The y-axis represents the interference score in milliseconds (mismatch-match)].

- Placebo: Green bar
- Estradiol Alone: Yellow bar with an asterisk
- Estradiol + Cortisol: Blue bar with an asterisk
- Cortisol Alone: White bar

Legend: GREEN, BLUE, YELLOW
Self-Ordered Pointing Test
Self-Ordered Pointing Test
Self-Ordered Pointing Test
Self-Ordered Pointing Test

Total Errors (Adjusted for Baseline & Time to Complete Task)

- Placebo
- Cortisol Alone
- Estradiol Alone
- Estradiol + Cortisol

Estradiol Alone has a significant effect compared to Placebo.
Story Recall

Information “Bits” Recalled
Change from Baseline

- Placebo
- Cortisol Alone
- Estradiol Alone
- Estradiol + Cortisol
Delayed Match-to-Sample

Study

Immediate Recall

Delayed Recall
Delayed Match-to-Sample

Errors (Max=10):

Change from Baseline

0 0.5 1 1.5

Placebo  Cortisol Alone  Estradiol Alone  Estradiol +Cortisol

*
IGF & Aβ
Summary: Cognitive Effects

- 2 months of estradiol, without elevated cortisol, has a beneficial effect on executive function for healthy postmenopausal women.
- Estradiol appears to benefit verbal memory independent of cortisol levels.
- 4 days of cortisol use impairs performance on select executive function tasks.
- Clear evidence for an interactive effect of estradiol & elevated cortisol on cognition ... combined regimen <> effects of cortisol & <> effects of estradiol.
As expected, 4 days of cortisol increases IGF-1; trend indicating decreased levels for estradiol-treated subjects; combine regimen appears to mimic effects of cortisol administration.

8 weeks of estradiol increases $\alpha_\beta 40$; 4 days of cortisol alters both $\alpha_\beta 40$ & $\alpha_\beta 42$ levels; again, the combined regimen appears to mimic effects associated with cortisol administration.
Future Directions

- Take a closer look at the parameters of “stress” that may interact with estradiol use
- Examine specific task demands that may be differentially affected by estradiol and cortisol
- Assess interactive effects for older adults who are beginning to manifest symptoms of cognitive impairment
- Continue to explore the αβ-IGF-cortisol relationship as a potential contributor to cognitive response to estradiol
Collaborators

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