2ND ANNUAL CHAIRS IN PSYCHIATRY SUMMIT
The Master Class for Psychiatric Professional Development
Reproductive Hormones and Depression…Huh?
A Rational Basis for Hormonal Psychopharmacotherapeutics

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Learning Objective

Name 2 ways in which estrogen level influences neural function in women
Reproductive Steroids: Sources of Variance and Context Dependency
Conversion of Cholesterol to Steroid Hormones

Metabolism Determines Function

E₂ = estrogen; ER = estrogen receptor; ERE = estrogen-responsive elements
Estradiol and ER
Manifold Regulators of Transcription

Coregulators Determine Effects of ER

Shape of Hormone Selects Receptor Coregulator

The two main components of the epigenetic code

DNA methylation
Methyl marks added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the ‘tails’ of proteins called histones. These alter the activity of the DNA wrapped around them.
Nucleosome

Histone Modifications Modulate Chromatin Structure

Estrogen Receptors and Depression

- $E_2$-induced arousal\(^1\)
- ER-beta knockout mouse – anxious\(^2\)
- Selective ER-beta modulators are anxiolytic\(^3,4\)
- ER-beta mediates antidepressant effects of $E_2$ in forced-swim test\(^5\)

Models of Depression

- Neurotransmitter deficiency
- Neuroplasticity
- Cellular energetics
- Stress/CRH
- Signal trafficking (e.g., p11)
- Inflammation
- Network dysregulation

CRH = corticotropin-releasing hormone (cortisol)
Endocrinology of...Fat?

Fat Orchestrator of Systemic Illness

Weight gain → Adipose tissue inflammation
Oxidative stress
ER-stress
Endothelial damage
Free fatty acids
Adipocyte necrosis

Macrophage recruitment
Secreted factors i.e. MCP-1, SAA

TNFα, JNK, IKKβ, IL-6, IL-1β, TLRs

## Relationship Between Inflammation, Disease, and Hormone Level

<table>
<thead>
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<th>CVD</th>
<th>Diabetes</th>
<th>Obesity</th>
<th>Depression</th>
<th>Stress</th>
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CVD = cardiovascular disease; IL-6 = interleukin-6; MCP-1 = monocyte chemoattractant protein-1; TNF-α = tumor necrosis factor alpha; VEGF = vascular endothelial growth factor
Models of Depression

- Neurotransmitter deficiency
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Conceptual Proposal for Relationship Between Anatomical Sites, Neural Computations, and Behaviors

rCBF Activation During Hormonal Manipulation

Leuprolide Alone  Leuprolide + Estrogen  Leuprolide + Progesterone

Working Memory Activation

Primary Motor & Visual Activation

rCBF = regional cerebral blood flow
Berman KF. *Proc Natl Acad Sci USA* 1997;94:8836-8841.
OFC Activity in Response to Emotional Stimuli in the Context of Behavioral Inhibition Across the Menstrual Cycle

NoGoNE = negative no-go; NoGoNU = neutral no-go; NoGoPO = positive no-go;
OFC = orbitofrontal cortex
Anticipation of Reward and Reward-Induced Activation Are Greater in the Follicular Phase

Follicular Phase
Correlations with Estradiol Level During Anticipation of Uncertain Rewards

Positive correlation with estradiol

Negative correlation with estradiol

Bilateral amygdalo-hippocampal complex

Hypothalamus

Follicular Phase

Positive Correlation with Estradiol Level at the Time of Rewarded Outcome

Bilateral dorsolateral prefrontal cortex

Bilateral fronto-polar cortex

Antidepressant Efficacy of Estradiol

- Estradiol is effective in perimenopausal women\(^1\)

- Estradiol is NOT effective in postmenopausal women\(^2\)

Hormone Psychopharmacology

- Psychotropic neuropharmacology
- Formulation
- Administration
- Indication
Hormone Psychopharmacology

- Psychotrophic neuropharmacology
- Formulation
- Administration
- Indication
Functional implications of structural differences
- \( E_2 \) vs. conjugated estrogens
- Progesterone vs. medroxyprogesterone

Measures of action: single tissues in isolation
Psychototropic neuropharmacology

Formulation

Administration

Indication
Hormone Administration

- Implications of route of administration
- Bioavailability
  - Absorption, distribution, protein binding, metabolism
- Individual differences, gender, and age
Hormone Psychopharmacology

- Psychotropic neuropharmacology
- Formulation
- Administration
- Indication
Women’s Health Initiative
The Good, the Bad, and the Ugly
16,608 **apparently healthy** postmenopausal women (50-79)
- ½ receive conjugated estrogens and medroxyprogesterone

**CHD = primary outcome**

**Invasive breast cancer = primary adverse outcome**

CHD = coronary heart disease
“This is the final nail in the coffin for hormone replacement therapy.”

Lori Mosca, MD, MPH, PhD
Director, Preventive Cardiology, New York-Presbyterian Hospital
Science, March 5, 2004

Science 2004;303:1449.
If $E_2$ is so “good for you,” why are they saying such terrible things about it?
1. Timing
Time-Dependent Protective Effects of E_2 Against Ischemic Brain Injury

MCAO = middle cerebral artery occlusion; OVX = ovariectomized females
Immediate E$_2$ Treatment Attenuated Proinflammatory Responses in the Brain

VEGF = vascular endothelial growth factor
2. Healthy Cell Hypothesis
How Do We Get from Gene to Gonadal Steroids to Depression?

- Animal models: the ER in depression
- Brain imaging: functional effects of $E_2$
- $E_2$: antidepressant efficacy
- **Modulation of gene expression by gonadal steroids**
  - Change in hormone as trigger
  - Genetic predispositions modified by gonadal steroids
- Stress, gonadal steroids, and epigenesis
A drug can be an inert substance, a poison, or a therapeutic agent depending upon how it is used and the dosage in which it is given.

Alle Ding' sind Gift und nichts ohn' Gift; allein die Dosis macht, dass ein Ding kein Gift ist.

"All things are poison and nothing is without poison, only the dose permits something not to be poisonous."

Paracelsus, 1493-1541.
We Don’t Know…

- Optimal combo of formulation, route, regimen, dose
- Mechanisms of harm
- Long-term risks
- Usefulness of protectors (e.g., statins)
- Risk to benefit of CS-EPT vs. CC-EPT
- Interactions with antidepressants
- Role in DM or HT
- Impact of different progestins
- Predictors of benefit or risk.............

CC-EPT = continuous-combined estrogen-progestogen therapy;
CS-EPT = continuous-sequential estrogen-progestogen therapy;
DM = diabetes mellitus; HT = hypertension
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Rocha BA, Fleischer R, Schaeffer JM, Rohrer SP, Hickey GJ. 17 Beta-estradiol-induced antidepressant-like effect in the forced swim test is absent in estrogen receptor-beta knockout (BERKO) mice. Psychopharmacology (Berl) 2005;179:637-643.


