If We Know So Much About Neurobiology, Why Do We Know So Little About Depression?

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Disclosures

- **Grants**: National Institutes of Health (NIH) (2 RO1s; T32); The Foundation of Hope Advisory Board

- **Advisory Boards**: Sage Therapeutics (Clinical Advisory Board); Sheppard Pratt-Lieber Research Institute (Scientific Advisory Board)

- **Other Financial or Material Support**: Editorial Board of Dialogues in Clinical Neuroscience
Explore the role of hormones in the neurobiology of depression.
Why Do We Know So Little About Depression?

- Diagnostic heterogeneity
- Associational studies
- Group data
- Stimulus-specific
- Cross-sectional physiology
- Context
Group Data

- Meaningful subgroups are ignored

Hmmm, I appear to be standing in warm water.
Why Do We Know So Little About Depression?

- Diagnostic heterogeneity
- Associational studies
- Group data
- Stimulus-specific
- Cross-sectional physiology
- CONTEXT
Physiology is Context-Dependent

- Developmental Stage
- Age
- Gender
- Species/tissue/cell
- Environment
- Genome
Context-Dependent (and Determining) Processes in Depression

- STATE
- SWITCH
- SUSCEPTIBILITY

How does the reproductive endocrine system help us understand these processes?
PMDD: A State Model

- Poor affective/behavioral modulation/inhibition
- Negative cognitive bias
- Amplified interpersonal sensitivity
- Disturbed social cognition
- Decreased reward
- Impaired state change
Daily Mood Ratings

Depression

AM

PM

Most Depressed

Most Happy

Menses

PATIENT 1

PATIENT 2

PATIENT 3

Menstrual Cycle Switch - Patient C.

Context-Dependent Affective Regulation: Reproductive Insights

- What is the signal?
- How do we account for variance in response?
- What are the determinants of the composition and regulation of affective state?
Steroid Cascade

Testosterone: Metabolism Determines Actions

Growth Factors
EGF
TGFα
IGF-1

Neurotransmitters
Dopamine

Hormones
E$_2$

Estrogen Receptors

Mitogen-activated protein kinase (MAPK)

CRE
APE
ERE
PRE

c-Jun/c-Fos
CREB
CBP/P300
SRC-1

Co Regulator

GR

E_R

Ca$^{++}$
cAMP
Akt
PI 2
Hormones

E2

Estrogen Receptor

CoReg

ERE

Courtesy of David Rubinow, MD
Estradiol-ER\(\alpha\)

Ligand Volume 250 Å\(^3\)
Actual Pocket Volume 450 Å\(^3\)

Courtesy of J. Katzenellenbogen
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Gonadal Steroids: A Window into Affective Dysregulation

- Why do we think that gonadal steroids have a role in affect regulation?
Models of Depression

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

How Does the Brain Work?

- Signal transmission and processing
- Clusters of neurons into networks: functional outcome
- Networks dynamically assemble
- Synchronization of neuronal firing conveys information
- Distributed neurons provide context

Estradiol Rapidly Induces Synaptic Connections

Models of Depression

- Neurotransmitter deficiency
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- Network dysregulation

Network Dysfunction in Depression

- Default Mode Network
- Social Cognition Network
- Reward Network
- Affective Regulation Network
- Salience Network

PMDD: A State Model

- Poor affective/behavioral modulation/inhibition (affective regulation network)
- Reduced social interaction; disturbed social cognition; amplified interpersonal sensitivity (social cognition network; salience network)
- Decreased reward (reward network)
- Impaired state change

As compared with ovarian suppression, estradiol replacement increases regional cerebral blood flow (rCBF) in regions of the default network, including the medial prefrontal cortex and precuneus.

\[ p = .005, \text{ uncorrected}; \text{Est} = \text{estradiol}; \text{Leup} = \text{leuprolide}; \text{Prog} = \text{progesterone} \]

Schmidt PJ, et al., Unpublished data.
Steroids Regulate Prefrontal Cortex Functional Correlations With Hippocampal Formation Activity

Self-stimulation of NTS mPOA Neurons Varies Across the Estrous Cycle

Optical self stimulation – 20 Hz

Is this effect modulated by steroid hormones? Magnitude of operant responding is highest in proestrous

Greater reward circuitry activation in the follicular phase: anticipation of uncertain rewards

Why think that gonadal steroids have a role in affect regulation?

- Modulate all pathophysiologic systems implicated in depression
- Modulate brain regions and networks disturbed in depression
- Antidepressant effects

E2 Efficacy in Treatment of Perimenopausal Depression

CES-D = Center for Epidemiologic Studies Depression Scale

Effect of Estradiol on Perimenopausal Symptoms

Time From Menopause Determines Effects of 17β-Estradiol (E2) on the Expression of Inflammatory Biomarkers in Uterine Arteries

A drug can be an inert substance, a poison, or a therapeutic agent dependent 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
Asymptomatic women with a past perimenopausal depression disorder (PMD) are responsive to estrogen.

Clinic visits (weekly)

Baseline W0 W3 W6 W7

PMD + = Asymptomatic women with a past perimenopausal depression disorder (PMD) are responsive to estrogen

E2 Withdrawal Precipitates Depressive Symptoms
But Not in Women With No History of Perimenopausal Depression (PMD)

E2 Continuous

E2 Withdrawal

PMD+ (n = 21)
PMD- (n = 12)

ANOVA-R: Dx*Tx* phase* week
F_{2,58} = 5.5, p < .01

CES-D = Center for Epidemiologic Studies Depression Scale
Efficacy of GnRH-A in the Symptoms of PMDD

GnRH-A = gonadotropin-releasing hormone agonist; PMDD premenstrual dysphoric disorder.

Steroid Precipitation of PMDD Symptoms

Endocrine Clamp Study

BID = twice a day; qd = every day

Baseline

Leuprolide (3.75 mg im)
Progesterone (200 mg BID)
Estradiol (100 µg qd)
Increase in symptoms over month
Effects of GnRH Agonist & Gonadal Steroid Replacement on PMDD

S & C Self-Rated Scores

S & C Rater Scores

Leuprolide (3.75 mg im)
Progesterone (200 mg BID)
Estradiol (100 µg qd)

Dutasteride is indicated for the treatment of benign prostatic hyperplasia in men with an enlarged prostate. This agent is not approved by the US FDA for the treatment of PMDD.

The Change is the Signal, but Only in the Context of Susceptibility

- Do reproductive steroids differentially affect brain regional activation in women with PMDD?
Differential Brain Regional Activation by Ovarian Steroids in PMDD

PMDD = premenstrual dysphoric disorder
Schmidt PJ et al., unpublished data.
DLPFC Overactivation in PMDD Correlated With Symptom-Related Impairment

DLPFC = dorsolateral prefrontal cortex; PMDD = premenstrual dysphoric disorder
PMDD: Significant Associations With SNPs Genotyped in *ESR1* (6q25.1)

ESC/E(Z) Complex Genes

Schmidt PJ, et al., Unpublished data.
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Questions & Answers