The Neurobiology of Depression:

Neurotransmitters, Neurosteroids, Neurotrophic Factors and Cell Aging

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Primary Questions

- How do Genetics, Early adversity and Stress each contribute to depression?
- How is stress transduced into depression?
- Is depression associated with neurotoxicity?
- Do stress and depression accelerate cell aging, leading to poor health?

Outline

The Neurobiology of Depression

- Genetic Vulnerability
- Early Life Adversity and Cumulative Stress
- Stress Hormones
- Neurosteroid Hormones
- Brain Growth Factors
- Cell Aging: Telomeres and Telomerase
Likelihood of Depression as a Function of 5HTT Genotype

Adapted from Caspi et al., 2003

Possible Mechanisms Linking ACE’s to Adult Pathology

• Behavioral, Psychological, Social Changes, High Risk Behaviors
• Epigenetic Transmission
• Biochemical Changes:
  – Changes in HPA Axis Activity
  – Neurotrophic Factors
  – Changes in the Telomere/Telomerase System

The LHPA axis

Depression may be a central nervous system response to high circulating cortisol levels
Differences in methylation emerged as early as one week of age, were reversed with cross-breeding, persisted into adulthood, inhibited transcription factor binding to the GR, and were associated with hyperactive stress responses. - Adapted from: Epigenetic programming by maternal behavior. Weaver I., Meaney M., Nat Neuroscience, 7: 847-54, 2004.

Depression may be a central nervous system response to high circulating cortisol levels.

Cortisol and the Brain:
Genomic Non-genomic
Trophic/Atrophic
Classical Steroids Neurosteroids

Glucocorticoid Potentiation of Ischemic Injury (Sapolsky & Pulsinelli, 1985)

Childhood Trauma Associated With Smaller HC Volume

Hippocampal Volume and Depression: A Meta-Analysis of MRI Studies

Videbech and Ravnkilde 2004

Vythilingam et al., 2002

Childhood trauma is associated with a smaller hippocampal volume compared to healthy controls.

Hippocampal volume (left, in mm³) in depressed women with or without a history of childhood physical or sexual abuse, compared to healthy controls.
Possible mechanisms for hippocampal volume loss in recurrent depression (Sheline, 2000)

According to this model, therapeutic strategies should include antidepressants, and stress reduction, exercise and environmental enrichment (increase BDNF and neurogenesis), phenytoin (prevent excitotoxicity), CRH antagonists and glucocorticoid inhibitors or blockers (lower glucocorticoid activity).

Glucocorticoid Antagonists

To the extent cortisol is involved in the pathogenesis of depression, treatments that lessen cortisol activity should have antidepressant effects.

Double-blind ketoconazole treatment of hypercortisolemia depression

Metyrapone as Additive Treatment in Major Depression

A Double-blind and Placebo-Controlled Trial

- N= 63
- Metyrapone vs. placebo, added to nefazodone or fluvoxamine
More mifepristone patients met the 50% “response” criterion on the BPRS Positive Symptom Subscale (psychosis), compared to placebo patients ($p=0.046$). No significant benefit was seen on the HDRS.

**Depression Sub-type**

<table>
<thead>
<tr>
<th>Response (50% HAM-D)</th>
<th>Mean Change HAM-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>All, combined</td>
<td>-</td>
</tr>
<tr>
<td>Non-psychotic (UP and BP)</td>
<td>+</td>
</tr>
<tr>
<td>Psychotic*</td>
<td>-</td>
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*In psychotic depression, there was no significant difference in response rate on the Total BPRS, but a significant advantage was found on the Positive Symptom Subscale of the BPRS.

“The use of anti-glucocorticoids in the treatment of mood disorders is at the proof-of-concept stage. Results in some diagnostic subtypes are promising and warrant further investigation to establish the clinical utility of these drugs in the treatment of mood disorders.”
Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA) seemingly has "anti-cortisol" effects as well as other effects of interest.

Chronic Stress Differentially Affects Steroid Levels

Dehydroepiandrosterone (DHEA) stimulates neurogenesis in the hippocampus of the rat, promotes survival of newly formed neurons and prevents corticosterone-induced suppression.
Double Blind DHEA Treatment of Depression

(Wolkowitz et al., 1999)

DHEA PLACEBO

30 25 20 15 10 5

HDRS Ratings

(N=11) (N=11)

DHEA, 90 mg/day, or Placebo, used alone or added to stabilized antidepressant, for 6 weeks.

DHEA Has Antidepressant Effects in Schizophrenia
(Strous et al., 2003)

Allopregnanolone:
A Potent GABA-A Receptor Agonist in the Brain
Concentrations of Cortisol and Allopregnanolone in Plasma of Patients with Major Depression and After Clinical Recovery
Adapted from Strohle et al., 1999

Units: nmol/L cortisol x 10^-2

Neuroprotection vs. Neurotoxicity

- Allopregnanolone is a highly potent GABA-A receptor agonist in the brain
- SSRI's (but not non-SSRI's) increase allopregnanolone concentrations within minutes
- SSRI's have unique anti-anxiety effects and ability to acutely treat PMDD by virtue of increasing the progesterone metabolite GABA-A receptor agonist, allopregnanolone

- DHEA
- Allopregnanolone
- BDNF
- Telomerase
- Cortisol
- Telomere Attrition
Modified from Duman et al. 
*Neuronal survival and mood disorders*; *Biol Psychiat* 2000; 48: 732-9

Antidepressants and ECS Increase HC Neurogenesis

Malberg et al., 2000

Does Depression Lead to Premature Aging?
Telomeres and telomerase

- Telomeres are non-coding sequences capping DNA ends that can shorten with somatic cell divisions and serve as a “senescence clock” (a marker of biological age)
- Telomerase is a cellular enzyme that forestalls telomere shortening and has additional non-telomeric roles in cell survival.

Although average telomere length declines with age, note the high degree of inter-individual variability, which remains largely unexplained.

Study Design:
- 39 mothers of chronically ill children (“stressed” group)
- 19 mothers of healthy children (control group)
- Ages 20-50 y.o. All analyses controlled for age
- PBMC telomere length by PCR
- Telomerase by Telomerase Repeat Amplification Protocol

The Telomere Team

Elizabeth Blackburn, Ph.D.
Elissa Epel, Ph.D.
Jue Lin, Ph.D.
Telomere Length

Telomerase Activity

**High stress women showed signs of cellular aging comparable to non-stressed women ~ 13 years older!**

**Telomere Shortening and Mood Disorders: Preliminary Support for a Chronic Stress Model of Accelerated Aging**

44 patients and 44 controls. Patients' telomere lengths were shorter, on average, by 660 base pairs (~10-20 years)

**Pilot Study: Depression is Associated with Telomere Attrition and Elevated Telomerase Activity**

Wolkowitz et al., unpublished data

**Pilot Study: Adverse Childhood Events (ACE) are Associated with Telomere Attrition in Adults**

<table>
<thead>
<tr>
<th>Total ACE (all subjects)</th>
<th>↓Telomere Length</th>
<th>↑Telomerase Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r= -0.29, p&lt;0.10, n=20</td>
<td>r= 0.50, p&lt;0.004, n=25</td>
</tr>
</tbody>
</table>

• p values are one-tailed
• Pooled controls and depressed subjects
• Correlations held even when depressive severity was factored out
• The specific type of ACE that most strongly correlated with cell aging parameters was sexual abuse

Wolkowitz et al., unpublished
Does Cell Aging cause CVD in Depression?

Telomeres and CVD risk

Shorter telomeres are reported in multiple medical illnesses, including:

- CAD, Myocardial Infarction
- Diabetes
- Vascular dementia
- Obesity, insulin resistance

REFERENCES:

Telomere Length and Survival

Cawthon et al studied 143 normals > 60 y.o. Individuals with shorter telomeres had poorer survival (OR= 3.18, heart disease).

Mechanisms by Which Depression May Lead to Cardiac Events (Mary Whooley, JAMA, 2006)

Potential biological mechanisms:
- Alterations in cardiac autonomic tone
- Common genetic vulnerability
- Enhanced activity of the HPA axis
- Greater patient activation
- Increased catecholamine levels
- Increased whole blood serotonin
- Inflammatory processes
- Lower omega-3 fatty acid levels
- Mental stress-induced ischemia

Potential Behavioral mechanisms:
- Dietary factors
- Lack of exercise
- Medication non-adherence
- Poor social support
- Unhealthy lifestyle
Other mechanisms being investigated include oxidative stress and pro-inflammatory cytokines, among others.

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- Lori Kans
- Tom Everhart
- Alanie Lazaro
- Genevieve Manalo

**Questions?**
Antidepressants and ECS Increase HC Neurogenesis

Mallberg et al., 2000