Obesity, Inflammation, and Depression: When Psychiatric and Medical Factors Collide
Learning Objectives

• Identify the relationship between depression and medical factors (inflammatory, endocrine, and metabolic)

• Consider comorbid medical conditions when selecting treatment for patients with depression

• Assess the potential utility of biomarkers in the diagnosis and treatment of depression
Pretest Question 1

A 36-year-old man with major depressive disorder is having lab work done to assess his levels of inflammatory markers. Based on the current evidence regarding inflammation in depression, which of the following results would you most likely suspect for this patient?

1. Elevated levels of tumor necrosis factor-alpha (TNF-alpha)
2. Reduced levels of interleukin 6 (IL-6)
3. Both 1 and 2
4. Neither 1 nor 2
Pretest Question 2

The patient's lab work comes back indicating elevated levels of tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6). Elevated cytokine levels may indirectly lead to:

1. Excessive glutamate neurotransmission
2. Excessive GABA neurotransmission
3. Reduced glutamate neurotransmission
4. Reduced GABA neurotransmission
Pretest Question 3

A 21-year-old man presents with his first major depressive episode. His medical history is significant for obesity (BMI 32). After ruling out any history of bipolar illness, his clinician elects to begin treatment with an antidepressant. What is true regarding the relationship between obesity and the likelihood of response to antidepressants?

1. Obesity increases the likelihood of response
2. Obesity has no effect on the likelihood of response
3. Obesity reduces the likelihood of response
Disease Models in Mood Disorders

- Monoamine hypothesis
- Inflammatory hypothesis
- Excitotoxicity hypothesis
- Neurotrophic hypothesis
- Cellular-metabolic hypotheses
What Does Inflammation Have to Do With Depression?

Inflammation

- IL-6
- TNF-α
- IFN-γ

Depression

- Altered monoamine synthesis
- Increased glutamate activity
- Increased oxidative stress
- Reduced neurotrophic support
- Reduced neurogenesis
- HPA axis disturbances

Chronic Low-Grade Inflammation Can Affect Neurotransmitter Synthesis

- Tryptophan
  - IDO
  - IL-6
  - TNF-α
  - IFN-γ
  - TRY OH
  - 5HTP
  - AAADC
  - 5HT

- Kynurenine
  - Quinolinic acid (NMDA agonist)
  - Glu, oxidative stress

Miller AH et al. Biol Psychiatry 2009;65(9):732-41;
Chronic Low-Grade Inflammation Can Affect Neurotransmitter Synthesis

Chronic Low-Grade Inflammation Can Affect Neurotrophic Support and Neurogenesis

HPA Axis Stress Response

Interaction Between Endocrine and Inflammatory Factors

- Stressor
- Increased CRF
- Increased ACTH
- Dysregulation of glucocorticoid receptors
- Increased glucocorticoids

HPA Axis Changes in MDD

- Stressor
- Dysregulation of glucocorticoid receptors
- Increased glucocorticoids
- Hypothalamus
- CRF
- Pituitary
- Reduced hippocampal volume
- Adrenal gland
- ACTH
- Increased CRF
- Increased ACTH

Varicella zoster virus–specific responder cell frequency (VZV-RCF) results at baseline, 6 weeks, 52 weeks, and 104 weeks in non-depressed controls, depressed patients who are not being treated with antidepressants, and depressed patients who are being treated with antidepressants.
What Does Inflammation Have to Do With Obesity?

- White adipose tissue (main site for fat storage) contains adipocytes that secrete hormones and inflammatory cytokines

- IL-6, TNF-alpha, and CRP are consistently elevated in obesity (chronic low-grade inflammatory state?)

- Upregulation of kynurenine pathway in obesity

What Does Obesity Have to Do With Depression?

Obesity

Depression

Neurotransmitter imbalances
Dysregulated inflammatory pathways
Increased oxidative stress
Reduced neurogenesis
HPA axis disturbances

What Does Obesity Have to Do With Depression?

- Daumit et al. 2003: 29% of men and 60% of women with severe and persistent mental illness were obese compared to 17.7% of men and 28.5% of women in the general population.
- Dickerson et al. 2006: 50% of women and 41% of men with psychiatric illness were obese compared to 27% of women and 20% of men in a non-psychiatric matched comparison group.
- Luppino et al. 2010: meta-analysis of 15 longitudinal studies showed that depression was associated with increased rates of obesity.
- Abdominal obesity in particular may be characteristic of depression (Carpiniello et al. 2012; Rivenes et al. 2009; van Reedt Dortland et al. 2013).

Metabolic Markers in Depression

• BMI
  – Higher BMI $\rightarrow$ higher risk of depression
  – Depression $\rightarrow$ higher risk of increased BMI

• Leptin
  – Low levels $\rightarrow$ depressive symptoms*
  – Acute administration $\rightarrow$ antidepressant response

• Omega-3 fatty acids
  – Reduced total, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) in depression

Obesity and Depression

• Baseline obesity predicts subsequent depression (and vice versa)\(^1,2\)

• Higher BMI is linked to increased prevalence, severity, and chronicity of depression\(^3\)

• Obesity reduces response to antidepressants\(^4,5\)

• Diet and exercise interventions reduce depression in obese, medically ill patients\(^6\)

Interaction Between Metabolic, Endocrine, and Inflammatory Factors

- Diabetes and metabolic syndrome are associated with abnormal HPA activity
- Leptin is decreased by chronic stress; ghrelin is increased by chronic stress
- Expanded adipocytes → oxidative stress and increased proinflammatory cytokines
- BMI positively correlates with IL-6 and hsCRP
- Exercise reduces inflammatory markers

Clinical Implications
Have We Identified Inflammatory, Endocrine, or Metabolic Biomarkers?

• Now
  – None?

• Projected
  – Select initial treatment
    • Positive, negative, or prescriptive moderator
  – Change/maintain treatment
    • Mediator; ideally changes prior to clinical improvement, allowing treatment decisions to be made earlier
  – Design clinical trials
Preliminary Data: Body Mass Affects Treatment Response in Depression

Fig. 1. Scatter plot of the association between the baseline body weight and the 17-item Hamilton Depression Rating Scale (HAMD-17) reduction at the end point

Preliminary Data: BMI Affects Treatment Response to L-methylfolate

**BMI <30**
- HDRS-28: n=32, p=0.648
- CGI-S: n=32, p=0.391
- HDRS: n=32, p=0.391
- Effect Size: 0.14

**BMI ≥30**
- HDRS-28: n=40, p=0.001
- CGI-S: n=40, p<0.001
- HDRS: n=40, p<0.001
- Effect Size: -0.75

Fava M et al. Oral presentation at NCDEU 2012.
L-methylfolate in Depression Stratified by Biomarkers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pooled Mean Change vs. PBO</th>
<th>95% CI</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>Biomarker</strong></td>
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<tr>
<td>SAM/SAH≥2.71</td>
<td>-0.380</td>
<td>(-2.239, 1.479)</td>
<td>0.689</td>
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<td>SAM/SAH&lt;2.71</td>
<td>-2.398</td>
<td>(-4.312, -0.485)</td>
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<td>hsCRP≥2.25 mg/L</td>
<td>-1.668</td>
<td>(-3.843, 0.507)</td>
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<td>hsCRP&lt;2.25 mg/L</td>
<td>-1.918</td>
<td>(-3.637, -0.199)</td>
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<td>4-HNE≥3.28 mcg/mL</td>
<td>-2.471</td>
<td>(-4.483, -0.459)</td>
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<td>4-HNE&lt;3.28 mcg/mL</td>
<td>-0.796</td>
<td>(-2.579, 0.988)</td>
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<td><strong>Genetic marker</strong></td>
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<td>MTHFR 677 CC</td>
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<tr>
<td>MTHFR 677 CT/TT</td>
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<tr>
<td>MTR 2756 AA</td>
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<td>(-2.484, 1.221)</td>
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<td>MTR 2756 AG/GG</td>
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<td>(-5.881, -1.491)</td>
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Genetic Variants for Synthesis of L-methylfolate With Downstream Effects on Monoamines
Preliminary Data: CRP Level Affects Differential Treatment Response

Limitations With Using Biomarkers in Major Depressive Disorder

• Identified biomarkers are not specific to MDD
  – Biomarkers are also altered in disorders that are commonly comorbid with depression, even in the absence of MDD

• Identified biomarkers are neither necessary nor sufficient to cause MDD

• Panel of biomarkers rather than single biomarker may show clinical utility
Good response
• Reduced inflammatory markers during treatment

Poor response
• Increased inflammatory markers at baseline
• Increased inflammatory markers during treatment

Depressive Symptoms in Patients With Chronic Illness: Improved With Anti-inflammatory Strategies?

- Lethargy
- Decreased appetite
- Increased sleeping
- Decreased mood
- Decreased interest in activities
- Decreased sexual activity
Targeting Inflammation and its Effect: Neurotransmission

• Monoamine synthesis/BH4 pathway
  – L-methylfolate added to SSRI $\rightarrow$ superior to placebo
    • 2 trials
  – SAMe added to SRI $\rightarrow$ superior to placebo

• Glutamate/oxidative stress
  – Ketamine $\rightarrow$ rapid, short-term improvement in mood and suicidal ideation
    • Several other NMDA antagonists under investigation
  – N-acetylcysteine $\rightarrow$ preliminary positive data in bipolar depression

Targeting Inflammation and its Effect: Anti-inflammatory Strategies

- TNF-alpha antagonists
  - Etanercept superior to placebo for improving depressive symptoms in psoriasis (independent of disease improvement)
  - Infliximab (Raison et al. 2013)

- COX-2 inhibitors
  - Celecoxib added to reboxetine $\rightarrow$ superior to placebo
  - Celecoxib added to fluoxetine $\rightarrow$ superior to placebo

- Acetylsalicylic acid
  - Added to fluoxetine $\rightarrow$ increased remission rate (open-label)

- P38 MAPK cytokine signaling pathway
  - GW856553 $\rightarrow$ Phase II depression trial

Minocycline

• Second-generation, semi-synthetic tetracycline analog with antimicrobial properties

• Highly lipophilic; easily penetrates the BBB, in contrast to tetracycline

• Principal metabolite: 9-hydroxyminocycline (inactive)

The Role of GLP-1 in Neuronal Activity and Neurodegeneration

Effect of liraglutide on amyloid plaque count

Inflammation response (IBA-1 stain)

GLP-1: glucagon-like peptide 1.
Holscher C. Vitam Horm 2010;84:331-54.
Targeting Neuroendocrine Function

• Glucocorticoid receptor
  – Mifepristone (antagonist) → efficacy in open-label and placebo-controlled trials of psychotic depression (main effects on psychotic symptoms)

Targeting Metabolic Function

• Diet
  – Omega-3 fatty acids → meta-analysis shows positive evidence of efficacy in unipolar and bipolar depression; EPA is the effective component (vs. DHA)

• Exercise
  – Seems to reduce depressive symptoms
    • Possibly through an anti-inflammatory mechanism

Targeting Metabolic Function: Meta-analysis of Weight Loss Interventions

Studies evaluated reduction in depressive symptoms but in most cases did not include patients with MDD. Significant reductions in depressive symptoms occurred with intervention regardless of change in weight.

Exercise: Evidence of Efficacy

• Meta-analysis of 58 randomized trials
  – Moderate to vigorous exercise (aerobic or resistance) vs. control condition (no treatment or wait list control)
  – General population: significantly lower depression scores with exercise vs. control treatment (effect size: -0.80)
  – Clinically depressed population: significantly lower depression scores with exercise vs. control treatment (effect size: -1.03)
  – Aerobic exercise = resistance exercise

Emerging Evidence: Increased Remission Rates With Add-On Exercise

TREAD: patients with inadequate response to SSRI received add-on exercise (low: 4 kcal/kg/week or high: 16 kcal/kg/week)

NNT=7.8 for higher-dose exercise group


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Exercise: Cochrane Review

• Meta-analysis of 30 randomized trials in depressed population
  – Moderate clinical effect of exercise [pooled standardized mean difference (SMD): -0.67]
  – 4 trials (n=326) with adequate allocation concealment, intent-to-treat analysis, and blinded outcome assessment: small clinical effect (pooled SMD: -0.31)

Exercise and Hippocampal Neurogenesis

Aged rats

Place recognition memory

Presynaptic density

Connectivity

Exercise in Depression: Optimal Dose, Intensity, Duration?

- 10–16 weeks duration > 4–9 weeks duration
  - $p = 0.0273$

- 45–59 minutes > 30–44 minutes and 60+ minutes
  - $p = 0.0010$ and $p = 0.0122$

- 5 times/week > 2–4 times/week

- No significant differences across categories of exercise intensity (% maximum heart rate)

Summary

• Several potential biomarkers for depression have been found to be associated with onset and severity of depression as well as treatment response

• These include inflammatory, endocrine, and metabolic factors

• However, no single biomarker has predictive value

• Identification of these factors may ultimately lead to a panel of biomarkers as well as new treatment strategies targeting these biomarkers