Is Bipolar Disorder an Energy Disorder?
Evidence and Novel Treatments

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# Disclosure Statement

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<td>Other Income</td>
<td>MBL Publishing for past services as Editor-in-chief of CNS Spectrums; Slack Inc. for services as Associate Editor of Psychiatric Annals; Editorial Board, Mind Mood Memory, Belvior Publications</td>
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<td>ADURS, ASCP, Brain and Behavior Foundation Colvin Prize, University of Pisa, University of Wisconsin at Madison, University Texas Southwest at Dallas, Health New England and Harold Grinspoon Charitable Foundation and Eli Lilly and AstraZeneca, American Society for Clinical Psychopharmacology and Zucker Hillside Hospital and Forest and Janssen, Brandeis University, International Society for Bipolar Disorder</td>
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Outline

- Mitochondria
- PPARS and PGC-1 alpha
- New treatments
We are made of stars.

Moby
FIGURE 2.
The cortical areas associated with the highest resting metabolic rates in the conscious resting state are located in the posteromedial parietal cortex (posterior cingulate cortex and precuneus, arrow)\textsuperscript{16}


Max=maximum; Min=minimum.

Mitochondria
Breathe
Eat
Energy
Mitochondria

- Provide energy
  - Produce Adenosine TriPhosphate (ATP)
    - Stores energy
  - Produce proteins and membranes
- Allow neurons to change
  - New neurons
  - New dendrites
  - New synapses
  - Regulate cell survival
  - Regulate cell death
Figure J-13: Electron Transport Chain

The electron transport chain is a series of protein complexes located at the inner membrane of the mitochondria.
Oxidative Stress
Oxidative Stress

• Natural Reactive Oxygen Species (ROS) from mitochondrial respiration
  – Superoxide anion
  – Nitric oxide
  – Hydrogen peroxide

• ROS can exceed metabolic capacity
  – Peroxynitrite
  – Hydroxy radical
Oxidative Stress

• Cellular dysfunction or death
• Non-physiologic ROS reactivity
  – Proteins
  – Nucleic acids
  – Carbohydrates
  – Lipids
• Due to dysfunctional electron flow in mitochondrial inner membrane
Oxidative Stress

- ROS damage mitochondria
- Decreased ATP and energy
- Damaged membrane
- Abnormal calcium sequestration
- Apoptosis (cellular death)
- Neurons especially susceptible
Mitochondrial Abnormalities in Bipolar Disorder

- Altered mitochondrial gene expression
- Decreased brain energy metabolism
- Altered calcium metabolism
- Bipolar calcium channel genes
- Decreased oxidative stress with lithium and valproate
PPARs and PGC-1 alpha
PPARs
(Peroxisome Proliferator Activated Receptors)

PGC-1 alpha
(PPAR Gamma Coactivator)
Peroxisome Proliferator-Activated Receptors

- Sit on DNA in nucleus
- Turn genes on and off
- Multiple functions
  - Regulate metabolism and fat
  - Anti-inflammatory and antioxidant
  - Protect neurons
PGC-1 alpha

• Key co-factor
  – PPARs
  – Estrogen related receptors (ERR)
  – Nuclear regulatory factors (NRF)

• Broad metabolic effects
  – Carbohydrate metabolism
  – Lipid metabolism
  – Mitochondria
  – Link between exercise and health
PGC-1α and mitochondria

- ↑ respiratory capacity
- ↑ mitochondrial enzymes
- ↑ electron transport chain complexes
- ↑ ROS
- ↑↑ ROS detoxification enzymes

protects from oxidative stress damage
(implicated in BD and neurodegenerative diseases)

interactions

↑ mitochondrial biogenesis

↑ peroxisomal biogenesis

metabolizes and export fatty acids to mitochondria

↑ PGC 1α

NRF

PGC-1α and mitochondria

↑ replication of mitochondrial genes

transcriptional factor

transcriptional factor

PGC-1α

NRF-1

TFA M

↑ respiratory capacity

↑ mitochondrial enzymes

↑ electron transport chain complexes

↑ ROS

↑↑ ROS detoxification enzymes

interactions
Can treatments that target PPARs help with bipolar disorder?
PPAR based treatments for Bipolar Disorder

• Anti-diabetic meds
• Anticholesterol meds
Anti-diabetic Thiazolidinediones (Glitazones)
Thiazolidinediones

• Increase *PPARG* expression and stimulate PPAR-gamma transcriptional activity in adipose tissue;
• Upregulate genes involved in lipid metabolism;
• Enhance the incorporation of free fatty acids (FFAs) into adipose tissue
• Decreases serum FFa levels

Kawai, M. & Rosen, C. J. *Nat. Rev. Endocrinol.* 6, 629–636 (2010);
Pioglitazone

• PPAR gamma agonist
• Decrease insulin resistance
• Decrease HbA1c
• Decrease HDL, TG, inflammation
• Secondary prevention
  – MI and CVA
  – MI with CKD
Pioglitazone in Major Depression

Pioglitazone for Major Depression

Sepanjnia et al. Neuropsychopharmacology (2012) 37, 2093–2100
Pioglitazone for bipolar depression with metabolic syndrome

Kemp et al. CNS Drugs (2014) 28:571–581

N=34

QIDS

Week 0

Week 8
Anti-cholesterol
Fibrates
Fibrates

- Old anticholesterol meds
  - Fenofibrate, clofibrate, gemfibrozil
- PPAR alpha agonists
- Neuroprotective
- Bezafibrate
  - Used for over 25 years in Europe
  - Safe
  - No weight gain
Bezafibrate

• Neuroprotective
  – Huntington’s
  – Parkinson’s
  – ALS
  – Traumatic Brain Injury
Bezafibrate Study

- Add to lithium for bipolar depression
- Measure
  - PGC-1 alpha gene expression
  - Mitochondria function
  - Brain Derived Neurotrophic Factor
  - fMRI brain circuits
  - Cognition
- Funding
  - Brain and Behavior Foundation Distinguished Investigator Award; Marriott Foundation
Exercise
“If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.”

Hippocrates
Why is exercise good for you?
Exercise increases PGC-1 alpha and decreases inflammation.

Handschin and Spiegleman. NATURE Vol 454 | 24 July 2008
↑ respiratory capacity
↑ mitochondrial enzymes
↑ electron transport chain complexes
↑ ROS
↑↑ ROS detoxification enzymes

protects from oxidative stress damage
(implicated in BD and neurodegenerative diseases)
Why is too much TV bad for you?
Inactivity plus obesity increases Inflammation.

Handschin and Spiegelman. NATURE|Vol 454|24 July 2008
Exercise

• Active muscles produce PGC-1 alpha
• PGC-1 alpha increases FNDC5
• FNDC5 increases Brain Derived Neurotrophic Factor (BDNF)
• BDNF
  – Brain fertilizer
  – Helps new and old neurons
• New neurons help with thinking
  – Increases ability to separate patterns
Sex and Family History Moderators of Exercise Augmentation for MDD

FH= Family history of mental illness; KKW=kilocalories/kg/week
Weight Loss/Obesity

- NEW Tx associated with nearly 10 lb weight loss (5.7% of body weight)
  - Associated with improved mood and quality of life
- Obesity associated with depression and poor quality of life
- Weight loss associated with improved depression, quality of life, and cognition

Transcranial
Near-Infrared Light
Transcranial Near-Infrared Light

- Passes through skull
- Stimulates mitochondria
  - Provides photon to cytochrome oxidase
  - Protects neurons
  - Anti-inflammatory
- Preliminary data for depression
- No studies of bipolar depression
- Collaboration with Paolo Cassano, MD
- Supported by BBRF and private donations
The electron transport chain is a series of protein complexes located at the inner membrane of the mitochondria.
Near Infrared Light for Depression

Summary

• Mitochondria as a target for bipolar disorder
• PPARS and PGC-1 alpha
• New interventions
  – Anti-diabetic and Anti-cholesterol meds
  – Exercise
  – Light – transcranial near infrared radiation
Thanks

• Eduardo Maia, MD
• Louisa G. Sylvia, PhD
• Brain and Behavior Research Foundation