Diet-Induced Metabolic Preconditioning of Brain Function and Plasticity through Epigenetics

Energy conservation crucial for brain evolution and for brain function

Efficient energy utilization

Diet and Exercise act as Epigenetic Modifiers

Extensive Gene Reprogramming

Building a Larger Brain
High gene susceptibility to metabolic alterations

Genomic changes
Disease diagnostic and treatment and control
Precision Medicine

- The human brain consumes 20–25% of the total energy in spite of small relative size to body.
- No surprise that the pathogenesis of many neurological disorders has an energy component

Fernando Gomez-Pinilla, UCLA
Metabolic Disorders Increase risk for many diseases

Top 10 leading causes of death in US, 2010

Heart disease
Cancer
Respiratory diseases
Stroke
Accidents
Alzheimer’s disease
Diabetes
Kidney Diseases
Influenza & pneumonia
Suicides

Percent of Obese (BMI ≥ 30) in U.S. Adults

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Epidemiological Considerations: metabolic disorders such as diabetes reduce threshold to neurological disorders

- Increased risk for neurological and psychiatric disorders (Am J Manag care 2007, 13 (7)).
- Diabetes is a significant predictor of poor outcome in neurological disorders such as Alzheimer’s (Profeno, Biol Psych., 2010) and trauma (Ley J, J Trauma 2011).
- Chronic obesity is associated with structural brain changes (Ho et al, Neurobiol Aging, 2010; Raji et al, Human Brain Map, 2010; Bryan et al, Radiology 2014).
- Diabetes and obesity are elevated in conditions associated with reduced mobility.
- Rise in consumption of sugars associated with the increased incidence of obesity in the general population (Hu & Malik, 2010; Malik et al., 2010).
- High-fructose corn syrup has become the sweetener most commonly added to processed foods (most sodas). Daily fructose intakes within the American diet average 37% of total sugars and 9% of daily energy.
How the balance between healthy and unhealthy foods affects CNS plasticity and function?

High caloric (Saturated fat and sugars)  
Omega-3 fatty acids  
Curcumin (turmeric)  

Exercise
Rise in consumption of sugars in the last 30 years and reduction in physical activity: temporally associated with the increased incidence of obesity in the general population (Hu & Malik, 2010; Malik et al., 2010)

What are the consequences for the brain?

Fernando Gomez-Pinilla, UCLA
Fructose consumption reduces hippocampal function and learning and memory capacity

Fernando Gomez-Pinilla, UCLA

Cisterna et al., BBADIS, BBA 2015
Fructose reduces hippocampal neurogenesis

A

B

C

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Cisterna et al., BBADIS, BBA 2015
**Many neurological disorders have a metabolic component**

**TBI is characterized by a period metabolic depression**

- Mild
  - GCS 15

- Severe
  - GCS 5

- Normal

Giza and Hovda, 2001

**Cell targets of the energy crisis:**
- Oxidative stress
- Membrane repair
- Synaptic plasticity
- Neuronal signaling

*Can nutrients provide broad protection?*

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Diet as vulnerability factor: How foods influence the capacity of the CNS to resist insults?

- concussive brain injury (fluid percussion injury, FPI)
Chronic fructose creates a state of vulnerability to reduce the outcome of TBI on pathways associated with metabolism and plasticity.

Agrawal et al, JCBFM, 2016
Can the effects of metabolic preconditioning be saved in the genes? Can the brain remember prior exposure to food?

Early DHA feeding preconditions adult plasticity

Fernando Gomez-Pinilla, UCLA

Tyagi et al, Neurobiol Dis, 2015
Epigenetic memory: Previous exposure to an n-3 diet protect against switching to a WD diet by reducing methylation of the bdnf gene

Exposure to the methylation inhibitor decitabine (DEC) blocked bdnf methylation

- Methylation of DNA occurs in about 80% of all CpG in mammals (about 80% of CpG are methylated).
- Methylation impacts transcription of genes by impeding binding of proteins or attracting binding of methyl-CpG-binding proteins

Tyagi et al, Neurobiol Disease, 2015
Systems Genomics allows a comprehensive understanding of the multitude of events involved in biology

- Gather systems level information
- Analyze and model data into tissue-specific networks for comprehensive understanding of physiology and disease

Have the instructional programs for all molecular, cellular, and organismal events

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The Power of RNA-seq to map the entire genome in detail

- RNA-Seq is used to analyze the continually changing cellular transcriptome.
- RNA-Seq facilitates the ability to look at several gene regulatory mechanisms such as alternative gene spliced transcripts, post-transcriptional modifications, gene fusion, mutations/SNPs and changes in gene expression.
- In addition to mRNA transcripts, RNA-Seq can look at different populations of RNA to include total RNA, small RNA, such as miRNA, tRNA, and ribosomal profiling.
Selective effects of fructose on DNA methylation in hypothalamic and hippocampal

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Meng et al. EBioMedicine 2016
Six degrees of separation theory postulates that everyone and everything is six or fewer steps away from any other person in the world, so that a chain of "a friend of a friend" can connect any two people in a maximum of six steps.

Network information is important to determine regulatory elements rather than secondary events.

Fernando Gomez-Pinilla, UCLA  
Collaborator Dr. Xia Yang, UCLA
Epigenetic Traits Organize in Gene Networks Affected by Fructose can be Normalized by DHA Intervention

Collaboration with Dr. Xia Yang

Fernando Gomez-Pinilla, UCLA
Tracing human pathologies using information from rodents: Genomic Wide Association Studies (GWAS)

Overlap between TBI network key drivers and human GWAS genes brain disorders/traits.

<table>
<thead>
<tr>
<th>GENE</th>
<th>Disease/Trait</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE1C</td>
<td>Smoking behavior</td>
</tr>
<tr>
<td>ANXA1</td>
<td>Schizophrenia, bipolar disorder and depression (combined)</td>
</tr>
<tr>
<td>CNTN4</td>
<td>Intelligence; Brain connectivity</td>
</tr>
<tr>
<td>COBL</td>
<td>Post-traumatic stress disorder</td>
</tr>
<tr>
<td>COL1A2</td>
<td>Intelligence</td>
</tr>
<tr>
<td>CPLX3</td>
<td>Coffee consumption</td>
</tr>
<tr>
<td>CXCL12</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>EGR2</td>
<td>Temperament</td>
</tr>
<tr>
<td>FBLN1</td>
<td>Temperament (bipolar disorder)</td>
</tr>
<tr>
<td>IRX2</td>
<td>Cognitive performance</td>
</tr>
<tr>
<td>NEUROD6</td>
<td>Major depressive disorder</td>
</tr>
<tr>
<td>NMU</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>PTPRO</td>
<td>Cognitive function</td>
</tr>
<tr>
<td>SERINC2</td>
<td>Alcohol dependence</td>
</tr>
<tr>
<td>SLC17A6</td>
<td>Autism spectrum disorder; ADHD; bipolar disorder, major depressive disorder, and schizophrenia (combined)</td>
</tr>
<tr>
<td>SP8</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>SYNE1</td>
<td>Bipolar disorder; Bipolar disorder and major depressive disorder (combined); Autism spectrum disorder, ADHD, bipolar disorder, major depressive disorder, and schizophrenia (combined)</td>
</tr>
<tr>
<td>UCN3</td>
<td>Intelligence</td>
</tr>
<tr>
<td>ZBTB18</td>
<td>Schizophrenia; Post-traumatic stress disorder</td>
</tr>
</tbody>
</table>

Table 1. Enrichment of human GWAS signals in HF signatures and KDs by SNP set enrichment analysis (SSEA).

<table>
<thead>
<tr>
<th>Tissue</th>
<th>GWAS Disease/Trait</th>
<th>GWAS study</th>
<th>p-value (KS test)</th>
<th>p-value (Fisher’s exact test)</th>
</tr>
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<tbody>
<tr>
<td>Hypothalamus</td>
<td>HDL cholesterol</td>
<td>GLGC</td>
<td>4.35E-05</td>
<td>1.25E-12</td>
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<tr>
<td></td>
<td>LDL cholesterol</td>
<td>GLGC</td>
<td>1.05E-03</td>
<td>1.90E-05</td>
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<tr>
<td></td>
<td>Total cholesterol</td>
<td>GLGC</td>
<td>8.51E-06</td>
<td>3.65E-14</td>
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<tr>
<td></td>
<td>Triglycerides</td>
<td>GLGC</td>
<td>5.88E-04</td>
<td>3.09E-09</td>
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<tr>
<td></td>
<td>Diastolic blood pressure</td>
<td>ICBP</td>
<td>2.40E-05</td>
<td>7.55E-05</td>
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<tr>
<td></td>
<td>Systolic blood pressure</td>
<td>ICBP</td>
<td>3.06E-03</td>
<td>1.16E-02</td>
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<tr>
<td></td>
<td>Type 2 diabetes</td>
<td>DIAGRAM+</td>
<td>2.07E-02</td>
<td>3.39E-02</td>
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<tr>
<td></td>
<td>Cognitive function</td>
<td>FHS</td>
<td>1.78E-02</td>
<td>3.18E-03</td>
</tr>
<tr>
<td></td>
<td>Bipolar disorder</td>
<td>WTCCC</td>
<td>3.06E-02</td>
<td>4.04E-02</td>
</tr>
<tr>
<td></td>
<td>HDL cholesterol</td>
<td>GLGC</td>
<td>6.48E-05</td>
<td>2.02E-07</td>
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<tr>
<td></td>
<td>LDL cholesterol</td>
<td>GLGC</td>
<td>2.98E-05</td>
<td>2.16E-04</td>
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<tr>
<td></td>
<td>Total cholesterol</td>
<td>GLGC</td>
<td>2.37E-05</td>
<td>4.19E-13</td>
</tr>
<tr>
<td></td>
<td>Triglycerides</td>
<td>GLGC</td>
<td>1.34E-02</td>
<td>6.55E-06</td>
</tr>
<tr>
<td></td>
<td>Diastolic blood pressure</td>
<td>ICBP</td>
<td>4.52E-01</td>
<td>4.59E-03</td>
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<tr>
<td></td>
<td>Systolic blood pressure</td>
<td>ICBP</td>
<td>9.43E-03</td>
<td>4.28E-02</td>
</tr>
<tr>
<td></td>
<td>Type 2 diabetes</td>
<td>DIAGRAM+</td>
<td>2.07E-02</td>
<td>3.39E-02</td>
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^ GLGC: Global Lipids Genetics Consortium; ICBP: The International Consortium for Blood Pressure; DIAGRAM+: The Diabetes Genetics Replication And Meta-analysis Consortium; FHS: Framingham Heart Study; WTCCC: Wellcome Trust Case Control Consortium; CATIE: Clinical Antipsychotic Trials for Intervention Effectiveness.

^ Bolded p values are those Bonferroni-corrected p < 0.05.
Preconditioning as a main predictable element for clinical diagnosis providing molecular basis for precision medicine

Clinical symptom

Disease phenotype

Organ Failure

Cellular Dysfunction

Molecular Dysfunction

Gene Program Changes

Traditional evidence oriented medicine

Molecular signature for Precision Medicine: Using longitudinal medical data as decision making tools for personalized medicine

Fernando Gomez-Pinilla, UCLA
Conclusions/implications:

• Metabolic preconditioning carried by diet impact fundamental gene regulatory mechanisms important for homeostasis and disease

• Changes in gene programming have the capacity to influence short- and long-term brain function and plasticity

• The impact of metabolic preconditioning on the genome provides basis for development of precision medicine strategies

• Epigenetic changes are inheritable. Tremendous implications for the mental health of future society.
Thanks NIH/NINDS, NIDA for support