Outline: Diet, Aging, and Mind

1. Brain Changes in Aging
2. Dementias
3. Dietary Interventions: Hormone-Like Compounds
   4. Androgen: DHEA
   5. Estrogens: Soy & Resveratrol
4. Summary and Conclusions
### Life Expectancy at Birth: United States

<table>
<thead>
<tr>
<th>Year of Birth</th>
<th>Both Sexes</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>1900</td>
<td>47.3</td>
<td>46.3</td>
<td>48.3</td>
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<tr>
<td>1960</td>
<td>69.7</td>
<td>66.6</td>
<td>73.1</td>
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<td>2005</td>
<td>77.8</td>
<td>75.2</td>
<td>80.4</td>
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</table>

National Center for Health Statistics (2008). CDC
## Average Weight & Height for Females & Males aged 18, 19, 20-29, & 50-59 Years: United States

<table>
<thead>
<tr>
<th>Age</th>
<th>Female</th>
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<th>Male</th>
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<tbody>
<tr>
<td></td>
<td>WT</td>
<td>HT</td>
<td>WT</td>
<td>HT</td>
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<tr>
<td>18</td>
<td>144</td>
<td>64</td>
<td>167</td>
<td>69.5</td>
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<tr>
<td>19</td>
<td>150</td>
<td>64</td>
<td>172</td>
<td>69.6</td>
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<tr>
<td>20-29</td>
<td>157</td>
<td>64</td>
<td>184</td>
<td>69.6</td>
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<tr>
<td>50-59</td>
<td>170</td>
<td>64</td>
<td>196</td>
<td>69.2</td>
</tr>
</tbody>
</table>

CDC (2005)
Global Obesity Epidemic

- 1,000,000,000 overweight
- 300,000,000 obese
- 40% elderly males obese or Type 2 Diabetes
- 45% elderly females obese or Type 2 Diabetes
- Increased risk CV Disease, Stroke, and Dementia
- Rising percentage of health care costs

WHO (2009); Ceska, 2007; NY Times, Nov 29
Obesity and Brain Structure

- Cardiovascular Health Cognition Study (n=927)
- Cognitively Normal Subjects (n=94; average age=77)
- BMI Calculated
  - normal = 18.5-25  overweight = 25-30  obese = 30+
- Volumetric Differences (Jacobian Map)

Raji et al (2009). Epub; Human Brain Mapping
BMI and Structural Volume

A: highlights the negative and positive correlations between BMI and brain structure projected onto the Cardiovascular Health Study Minimal Deformation Template (CHSMDT). Blue colors show stronger negative correlations. An inverse association between BMI and brain volume is observed in orbital frontal cortex (red arrow), the hippocampus (gold arrows) and subcortical areas (white asterisks) including the putamen, globus pallidus, and thalamus.

B: shows a P-value image of BMI main effects on brain structure projected onto the CHS-MDT. Dark colors indicate atrophy in both GM and WM; darker colors denote lower P-values.

Raji et al (2009). Epub; Human Brain Mapping
Correlation map (r-value image) effect sizes for a comparison of 14 obese persons (BMI > 30) to 29 normal weight persons (18.5–25). Obese persons had lower GM and WM volumes in the frontal lobes, anterior cingulate gyrus (a, blue arrow), hippocampus (b, black arrow), and basal ganglia (c, green box). Correlation coefficients range from 0 to 0.5.

Raji et al (2009). Epub; Human Brain Mapping
Everyone Please Stand Up
Changes with Aging

Younger

Older

Healthy knee joint

Osteoarthritis

Hypertrophy and spurring of bone and erosion of cartilage
Brain Aging: Normal

Basal Ganglia

The **basal ganglia** are clusters of nerve cells responsible for initiating and integrating movements. The basal ganglia become bright with age due to iron accumulation.

Subarachnoid Space

The **subarachnoid space** is the space around the outside of the brain. This area increases in size to fill the space with age-related cell loss.

White Matter

The **white matter** is a communication channel for the brain's information processing gray matter. White matter changes in appearance and may be related to the normal slowing of information processing in the brain with age.

www.omsi.edu/visit/life/aging/brainText.cfm
The **hippocampus** is the memory center of the brain. There is some cell loss associated with healthy aging, but this by itself does not indicate significant memory loss.

The **ventricles** are hollow spaces filled with cerebrospinal fluid. Like the subarachnoid space, these spaces increase in size as the brain becomes smaller with age.
Alzheimer’s Disease

- Memory loss
- Language deterioration
- Impaired ability to mentally manipulate visual information
- Poor judgment
- Confusion
- Restlessness
- Mood swings

*AD eventually destroys cognition, personality, and the ability to function*
Alzheimer's disease demonstrating significant cortical atrophy. Note the widening of the sulci and the narrowing of the gyri.

Normal brain half on the left and an abnormal half on the right. Note how much smaller the brain on the right and the effect on the hippocampus (arrow).
High-power views of neuritic plaques. The dense center of the plaque is the amyloid core, which is a magenta color on H&E (left) and brown on Bielschowsky (right). This amyloid is called beta-amyloid. Around the core are dystrophic neurites; these are the black strands you can see on the Bielschowsky stain (right). The dystrophic neurites contain neurofibrillary tangles made of tau protein.
Dietary Interventions
Marketed Benefits

CNS: Cognition/Memory, Libido, Well Being, Antidepressant, Neuroprotection, Decreased Impulsivity/Agitation

Peripheral: Cardiovascular, Immune System, Bone Density, Muscle Deposition, Skin Hydration

Burt Morrow
Lenore McDaniels
Everett Hosack
DHEA: Mechanism of Action

➤ Non-Genomic: Cell Surface

- GABA-A Receptor
  - CI⁻ Channel
  - Penatameric Structure: α, β, γ, δ, ε, ρ
  - Regional heterogeneity in Structure
  - Multiple Binding Sites
  - Direct and Indirect Effects

➤ Genomic: Transcription

- Androgen Receptor
  - Intracellular Trafficking
  - Transcriptional Activity
  - Ligand Dependent
Functional Assays

- Androgen Receptor: Immunochemistry
- AR Intracellular Trafficking: Confocal Microscopy
- DNA Microarray: Gene Regulation
- PCR: Microarray Validation
DHEA and DHT Upregulate AR in Female Mouse Brain

Ovariectomized female CF-1 mice were implanted with pellets containing DHEA (472 ug/day), DHT (72 ug/day), or placebo for 15 days. ICC for AR was conducted using PG-21 antibody according to methods in Lu et al. (1999).
CF-1 female mice were ovariectomized and treated S.C. with DHEA (0.5 mg daily release), T (0.1 mg daily release), or placebo pellet for seven days. AR immunoreactive cells are distributed only in the boundary of CA1 pyramidal cell layer.
3. INTRACELLULAR TRAFFICKING
Intracellular Trafficking: Time Course

**90 Minutes Post-treatment**

- **DHEA 10-5**
- **Adiol 10-6**
- **Adione 10-6**

Mo et al. (2006)
Nuclear Distribution of AR-GFP in COS-7 Cells Following Androgen or Androgen + Flutamide Treatment
Microarray Analysis
### Experimental Design

**Treatments**

<table>
<thead>
<tr>
<th>Control</th>
<th>DHEA</th>
<th>DHT</th>
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<tbody>
<tr>
<td>4 + 4 mice</td>
<td>4 + 4 mice</td>
<td>4 + 4 mice</td>
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</table>

**Samples**

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<thead>
<tr>
<th>Hypothalamus</th>
<th>Control</th>
<th>DHEA</th>
<th>DHT</th>
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<tbody>
<tr>
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<td>B1, B2</td>
<td>C1, C2</td>
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</table>

<table>
<thead>
<tr>
<th>Hippocampus</th>
<th>Control</th>
<th>DHEA</th>
<th>DHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1, D2</td>
<td>E1, E2</td>
<td>F1, F2</td>
<td></td>
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* Four brain regions were pooled to make one RNA samples
Heirarchical Cluster Analysis of Differentially Expressed Genes in Hypothalamus and Hippocampus

<table>
<thead>
<tr>
<th>Gene Name</th>
<th>DHEA/Veh Hypothalamus</th>
<th>DHT/Veh Hypothalamus</th>
<th>DHEA/Veh Hippocampus</th>
<th>DHT/Veh Hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepro-MCH</td>
<td>3.50</td>
<td>2.02</td>
<td>1.30</td>
<td>1.50</td>
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<td>Hypocretin</td>
<td>2.41</td>
<td>1.59</td>
<td>1.03</td>
<td>1.01</td>
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<tr>
<td>PKCδ</td>
<td>1.43</td>
<td>1.81</td>
<td>1.01</td>
<td>0.71</td>
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</table>
Real-time RT-PCR Analysis of Gene Expression in Mouse Hypothalamus

(a) Prepro-MCH at Hypo

(b) Orexin at Hypo

(c) PKCd at Hypo

(d) B2MT at Hypo
• DHEA is androgenic *in vivo* and *in vitro*

• The DHEA-AR complex acts as a transcription factor

• DHEA Alters AR-Mediated Gene Expression

• A cross-talk signaling pathway exists for DHEA in the CNS
Soy & Resveratrol
Dietary Soy Phytoestrogens and Agonistic Behavior in Male Cynomolgus Macaques

- N = 44 male cynomolgus macaques
- Low, high, or no soy isoflavone diet for 15 months
- Pretreatment observation for 8 weeks: aggressive, submissive, and affiliative behaviors
- Retest at end of diet: behavior and hormonal response to GnRH
Severe Agonistic Behavior in Cynomolgus Males fed Control or Soy Protein Diets containing 0.94(low) or 1.88 mg/g(high) isoflavone for 15 months

* p < 0.05 relative to C/L group.

Simon, N. et al. 2004
Resveratrol & Aging

- Flavonoid produced by grapes and some berries
- Might help explain the “French Paradox”
- Increased the lifespan of yeast, worms, fruit flies, fish, and mice fed high-calorie diets
- Chemical structure is very similar to diethylstilbestrol
- Target enzymes linked to aging process “sirtuins”
Resveratrol, Calorie Restriction, and Gene Expression

SIRT1 levels and Pgc1-a transcriptional activity in response to CR and resveratrol. (Left) SIRT1 levels brain (n = at least four animals per group) were determined by Western blot analysis. A loading correction factor based on HSP70 band intensity data was used to normalize the SIRT1 band intensity data. (Center, Right) mRNA abundance for known Pgc-1a transcriptional targets is shown for brain. Data on Y axis represent percentage changes relative to young controls. Results represent n = 5, values in bar graphs are means and SE.

Barger et al (2009)
Summary

- Soy & Resveratrol are estrogenic in vivo and in vitro
- The ER complex acts as a transcription factor
- Soy and Resveratrol Alter Gene Expression
- Effects are tissue-specific and receptor-subtype specific
Why is this Important?
Health and Social Issues
You Tube links

- [www.youtube.com/watch?v=zqfFrCUrEbY](http://www.youtube.com/watch?v=zqfFrCUrEbY) My generation The Zimmers 2:00 = The Who
- [http://www.youtube.com/watch?v=PUuUv5jos68](http://www.youtube.com/watch?v=PUuUv5jos68) resveratrol – Barbara Walters interview