DIET, AGING, and MIND

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Outline: Diet, Aging, and Mind

1. Review
2. Brain Changes in Aging
3. Dementias
4. Dietary Interventions: DHEA and Soy
5. DHEA
6. Soy
7. Summary and Conclusions
Male

Testosterone (T)

Steroid

E₂, DHT, T

Active

Metabolites

Serotonin

Vasopressin

Target System

INHIBIT

ENHANCE

Site of Action

5HT₁A, 5HT₁B

V₁A, AVP

Effect on Aggression

FACILITATION

Female

Dehydroepiandrosterone (DHEA)

Steroid

AE, DHEA

Active

Metabolites

Androgen Receptor

GABA

Regulated Transcription

An effect on aggression

Enhance

Enhance

INHIBITION
“I hope I Die Before I Get Old”

Pete Townshend

The WHO

“My Generation”
• www.youtube.com/watch?v=zqfFrCUrEbY
  My generation The Zimmers  2:18
• http://www.youtube.com/watch?v=i0XknwXqLD0&mode=related&search= The Who
  37 secs
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.

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.

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
Brain Aging: Normal

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.

www.omsi.edu/visit/life/aging/brainText.cfm
Social Cost of Dementias: $100 Billion/Year

- Significantly impaired intellectual functioning that interferes with normal activities and relationships.
- Inability to solve problems and maintain emotional control.
- Experience personality changes and behavioral problems, such as agitation, delusions, and hallucinations.
- Memory loss is a common symptom of dementia.
- Doctors diagnose dementia only if two or more brain functions - such as memory and language skills -- are significantly impaired without loss of consciousness.

Alzheimer’s disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Huntington’s disease, and Creutzfeldt-Jakob disease
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 Case History

- age 64 with a one month history of confusion, bizarre behavior, and insomnia.

- history of cardiac and pulmonary disease and depression, but no history of neurological disease.

- recently become obsessive about cleaning and organizing.

- Three days prior to admission he awakened in his car in a sitting position, was confused and disoriented and could not find his way home.

- On physical examination he was noted to have an unkept appearance with occasional bizarre behavior. (He was noted to wash his socks in the emergency room bathroom.)

- He was alert and oriented, with intact long-term memory.

- Neurological exam was notable only for decreased muscle bulk with normal tone and strength. Head CT and lumbar puncture were normal.

- He was diagnosed with manic depressive disorder and his moods stabilized with treatment. His cognitive decline was thought to be due to depression or early Alzheimer's Disease.

- At 66 said that his wife was having trouble getting him dressed and out of the house. He had decreased initiative and energy, and increased depression. On exam it was noted that his thoughts were not on target and he wandered easily between topics. He eventually was rehospitalized outside of UCSF for confusion and dementia.

- His diagnosis was thought to be "most likely Alzheimer's disease" and he was referred to support groups and prohibited from driving; day care was suggested. Eventually he was moved to a board and care facility where he died at age 71.
Alzheimer’s disease demonstrating significant cortical atrophy. Note the widening of the sulci and the narrowing of the gyri.
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

Supplements: $7 billion
- DHEA
- Soy $4 billion
  - $43 million
  - $4 billion
Dehydroepiandrosterone

Over the Counter Replacement Therapies

Soy Phytoestrogens
Annual Healthcare and Social Costs

- Dementias/Other Psychiatric Conditions: $100 billion
- Cardiovascular Disease: $56 billion
- Stress-Related Affective Illness: $40 billion
- Substance Abuse: $50 billion
DHEA and Soy: Marketed Benefits

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

**Peripheral:** Cardiovascular Tone, 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
    - Cl⁻ 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

- Interfemale Aggression
- Androgen Receptor: Immunochemistry and Western Blot
- Gene Expression: CAT Reporter
- AR Intracellular Trafficking: Confocal Microscopy
- DNA Microarray: Gene Regulation
- PCR: Microarray Validation
1. IN VIVO STUDIES IN FEMALE MOUSE
Females were ovariectomized, given DHEA or DHT for 19 days, and tested for aggression toward OVX females. Three hours after the test, the animals were sacrificed and brains were harvested for limbic system AR and ERβ determinations via Western blot.
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 (0.1mg daily release), or placebo pellet for seven days. AR immunoreactive cells are distributed only in the boundary of CA1 pyramidal cell layer.
2. GENE REPORTER ASSAYS
DHEA Metabolism

DHEA Sulfate

Sulfotransferase  Sulfatase

DHEA Sulfate

O

S

CH3

CH3

O

HSD

Dehydroepiandrosterone

3βHSD

Androstenedione

17βHSD

Testosterone

P450 aromatase

OH

OH

CH3

OH

7α-hydroxylase

7α-OH-DHEA

P450 aromatase

OH

OH

Estrone

Estradiol
DHEA and Major Metabolites: CAT Activity via AR

AR-mediated CAT activity induced by DHEA and its metabolites

Relative CAT Activity (Fold)

Veh
7α-OH-DHEA
7β-OH-DHEA
7-oxo-DHEA
DHEA-S
DHEA

Veh 7 6 5

Treatment Concentration: -$\log_{10}$ (M)

Involved plasmids: pSG5-AR, pMMTV-ARE-CAT

Mo et al., 2006
DHEA is androgenic

- Conferred AR transcriptional activity in a dose-dependent manner, and the effect was inhibited by flutamide.

DHEAS, 7α-, 7β-OH-DHEA and 7-oxo-DHEA are not androgenic
3. INTRACELLULAR TRAFFICKING
Intracellular Trafficking: Time Course

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

Androgen

10^{-7} M DHEA

10^{-7} M Adiol

10^{-7} M Adione

Androgen + Flu

DHEA + FLU

Adiol + FLU

Adione + FLU
Microarray Analysis
Genomic Analysis of DHEA- and DHT-Regulated Gene Expression in the Mouse Hypothalamus and Hippocampus

Experimental Design

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Control</th>
<th>DHEA</th>
<th>DHT</th>
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<tr>
<td>4 + 4 mice</td>
<td>4 + 4 mice</td>
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<table>
<thead>
<tr>
<th>Samples</th>
<th>Control</th>
<th>DHEA</th>
<th>DHT</th>
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<tbody>
<tr>
<td>Hypothalamus</td>
<td>A1, A2</td>
<td>B1, B2</td>
<td>C1, C2</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>D1, D2</td>
<td>E1, E2</td>
<td>F1, F2</td>
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</table>

* 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>
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</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>
</tr>
</tbody>
</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
Real-time RT-PCR Analysis of Gene Expression in Mouse Hippocampus

(a) Prepro-MCH at Hipp

(b) Orexin at Hipp

(c) PKCd at Hipp

(d) B2MT at Hipp

Cycle Number

Cycle Number

Cycle Number

Cycle Number
Summary

• DHEA inhibits female-typical, non-androgen dependent aggression

• Behavioral effects of DHEA and DHT differ, suggesting differences in mechanism of action

• DHEA is androgenic in vivo and in vitro

• The DHEA-AR complex acts as a transcription factor

• A cross-talk signaling pathway exists for DHEA in the CNS

DHEA Alters Androgen Receptor-Mediated Gene Expression
Soy and Behavior
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
Soy and Aggression: ERβ Mediation

- Isoflavones preferentially bind ERβ and are weaker agonists.
- ERβ is a negative modulator of ERα in several systems.
- ERα promotes agonistic behavior based on ERKO studies.
- Isoflavones may decrease 5-HT activity in dorsal raphe.
- Phytoestrogens Perturb CNS Function and Behavior.
Why is this Important?
Replacement Therapy: Male

That Sinking Feeling
Hair isn’t the only thing that falls with age; the hormones plentiful in youth also drop.

PERCENTAGE OF PRODUCTION IN MEN

25-34 35-44 45-54 55-64 65-74 75-84 85-100
100% 75 50 25 0

DHEAS Testosterone

*DEHYDROEPIANDROSTERONE SULFATE. SOURCE: N.Y. ACADEMY OF SCIENCE.

Soon after I inject myself with testosterone I feel a deep surge of energy. My attention span shortens. My wit is quicker, my mind faster, but my judgment is more impulsive.
Replacement Therapies: Female

Wyeth Bros Elixir

GeniSoy
SOY PROTEIN BAR
The Magic of Soy™

PREMARIN® (conjugated estrogens tablets, USP)
0.625 mg

PREMPRO™ (conjugated estrogens/dydrogesterone tablets)
0.625 mg / 2.5 mg

PREMPHASE® (conjugated estrogens/dydrogesterone tablets)
0.625 mg / 5 mg

PREMARIN® 0.625 mg (conjugated estrogens) VAGINAL CREAM in a nonliquefying base
Health and Social Issues

The Aging Mind
Alzheimer’s Disease & Normal Aging