DIET, AGING, & MIND

Neal G. Simon, Ph. D.
Dept. of Biological Sciences
Lehigh University

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
6. Summary and Conclusions

Life Expectancy at Birth: United States

Year of Birth	Both Sexes	Male	Female
1900	47.3	46.3	48.3
1960	69.7	66.6	73.1
2005	77.8	75.2	80.4

National Center for Health Statistics (2008). CDC

Average Weight & Height for Females & Males aged 18, 19, 20-29, & 50-59 Years: United States

Age	Female		Male	
	WT	HT	WT	HT
18	144	64	167	69.5
19	150	64	172	69.6
20-29	157	64	184	69.6
50-59	170	64	196	69.2

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

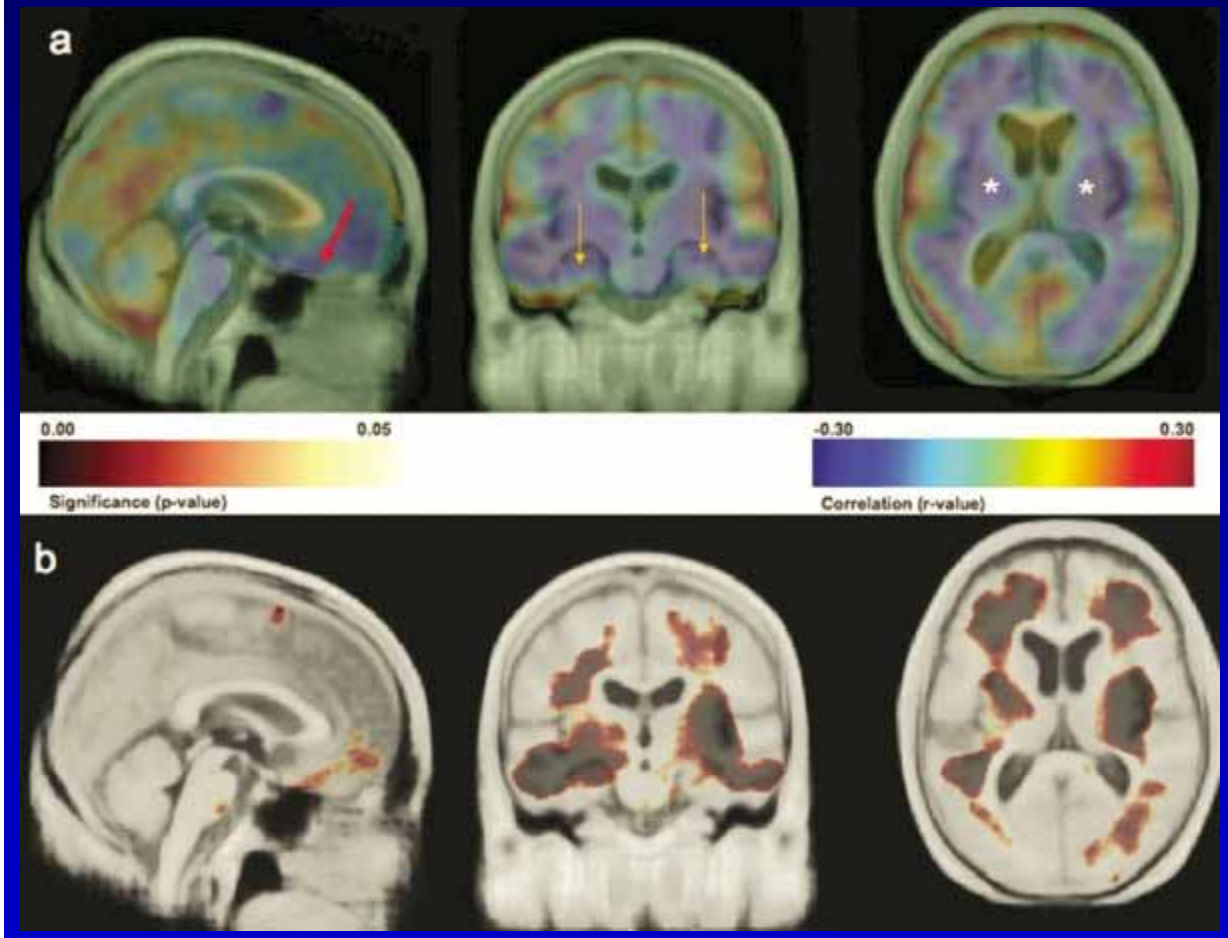
Obesity and Brain Structure

- 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

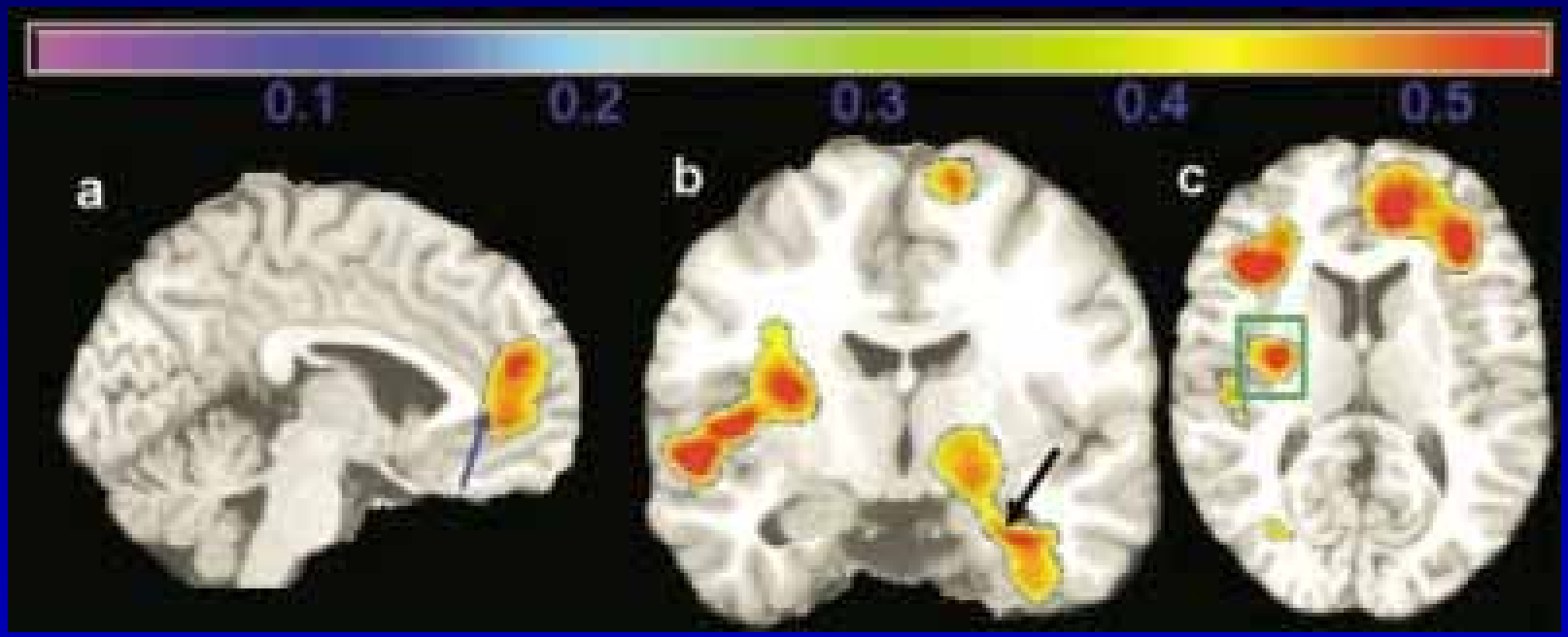


A: highlights the negative and positive correlations between BMI and brain structure projected onto the Cardiovascular Health Study Minimal Deformation Template (CHSMDT). Blue colors show stronger negative correlations An inverse association between BMI and brain volume is observed in orbital frontal 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

BMI and Structural Volume: Obese vs Normal

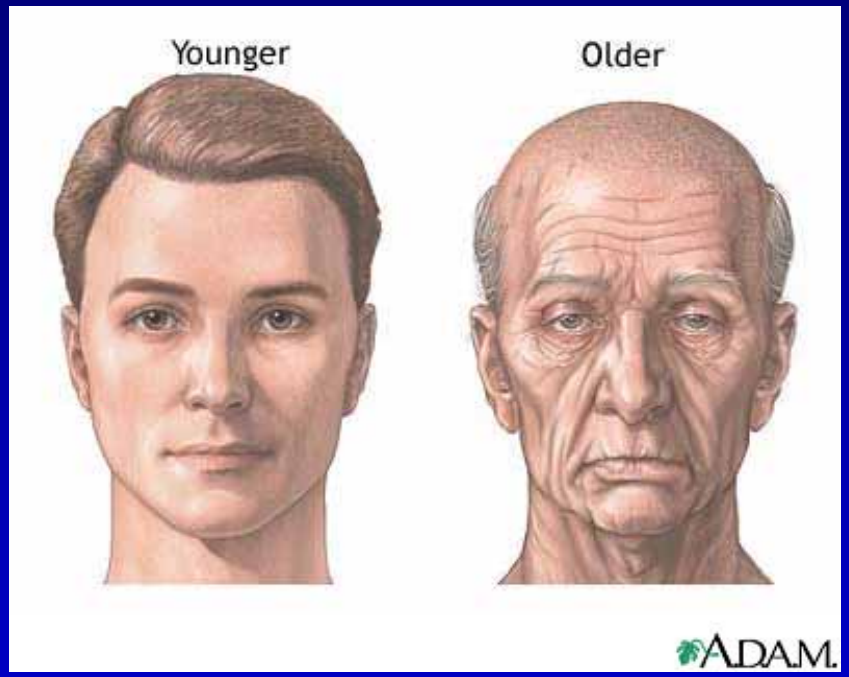


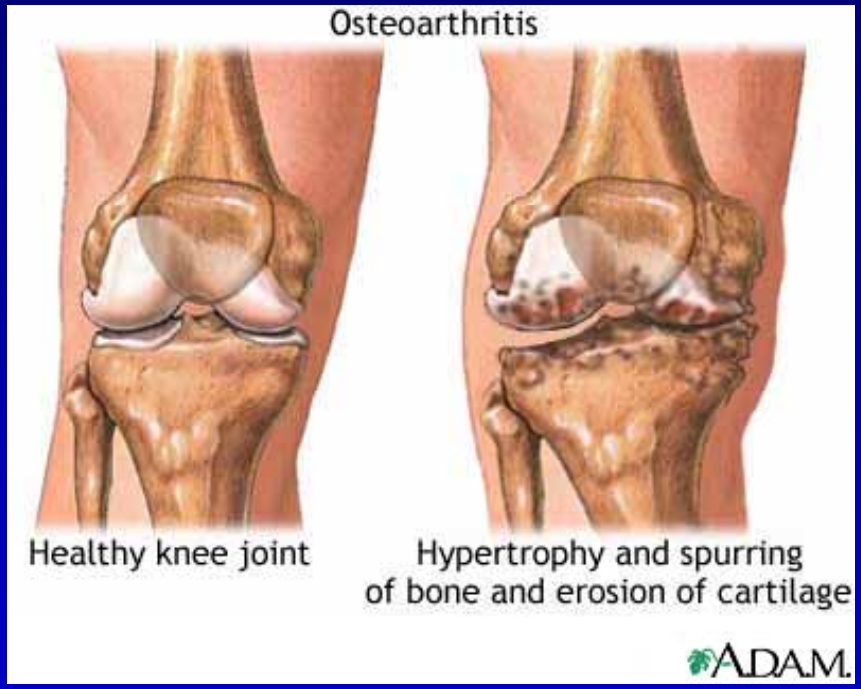
Correlation map (*r-value image) effect sizes for a comparison of* 14 obese persons (BMI > 30) to 29 normal weight persons (18.5–25). Obese persons had lower GM and WM volumes in the frontal lobes, anterior cingulate gyrus (a, blue arrow), hippocampus (b, black arrow), and basal ganglia (c, green box).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

Raji et al (2009). Epub; Human Brain Mapping

Everyone Please Stand Up

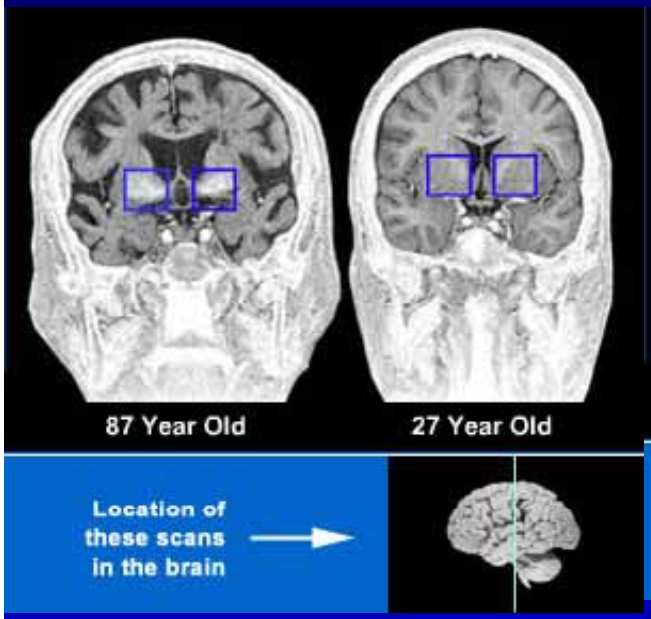
Changes with Aging





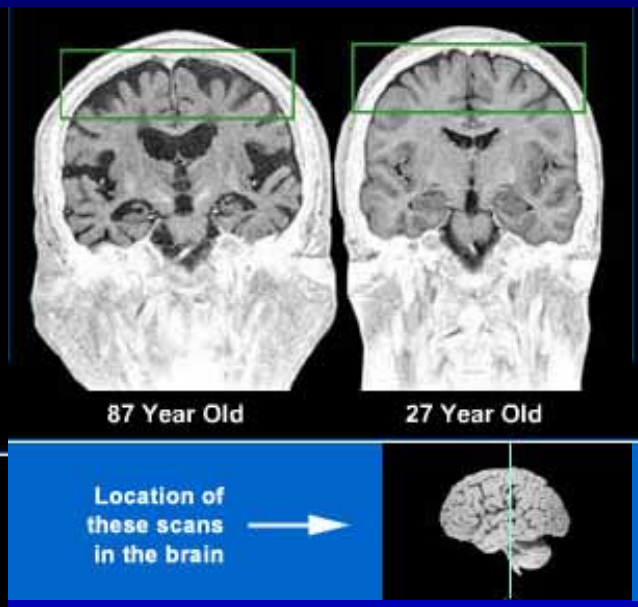
Brain Aging: Normal

Basal Ganglia



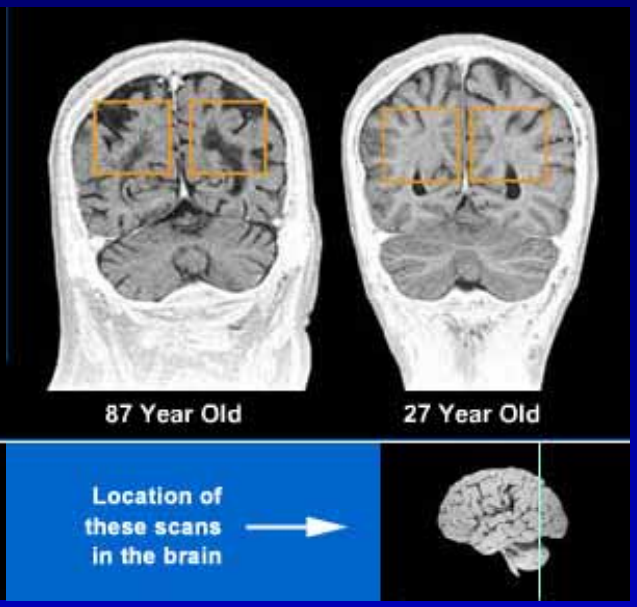
The **basal ganglia** are clusters of nerve cells responsible for initiatiting and integrating movements. The basal ganglia become bright with age due to iron accumulation.

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

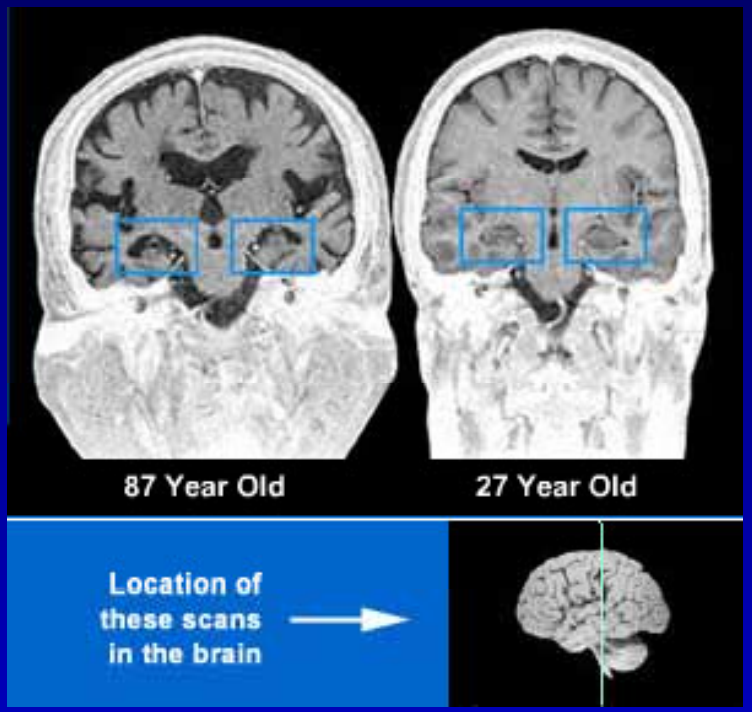
White Matter



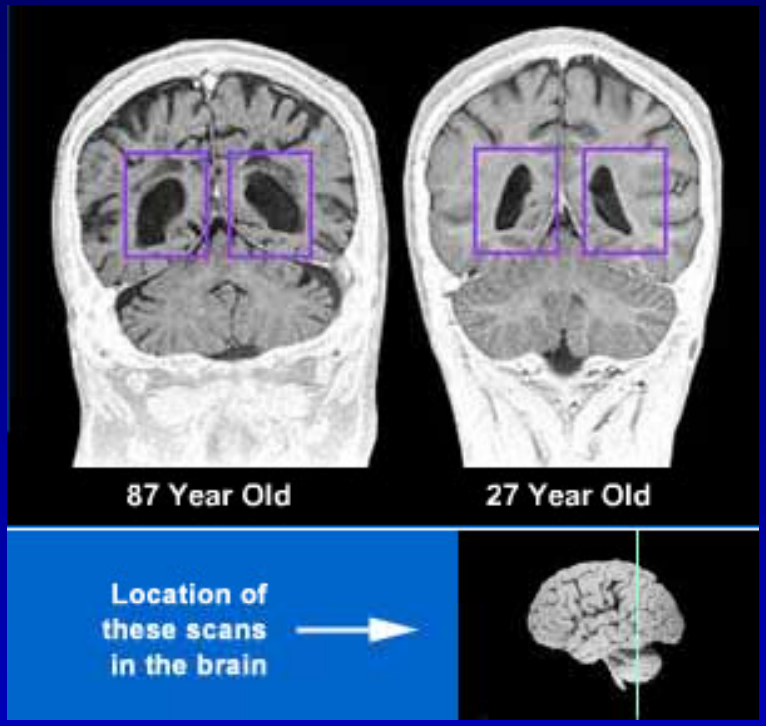
The **white matter** is a communication channel for the brain's information processing gray matter. White matter changes in appearance and may be related to the normal slowing of information processing in the brain with age.

www.omsi.edu/visit/life/aging/brainText.cfm

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.

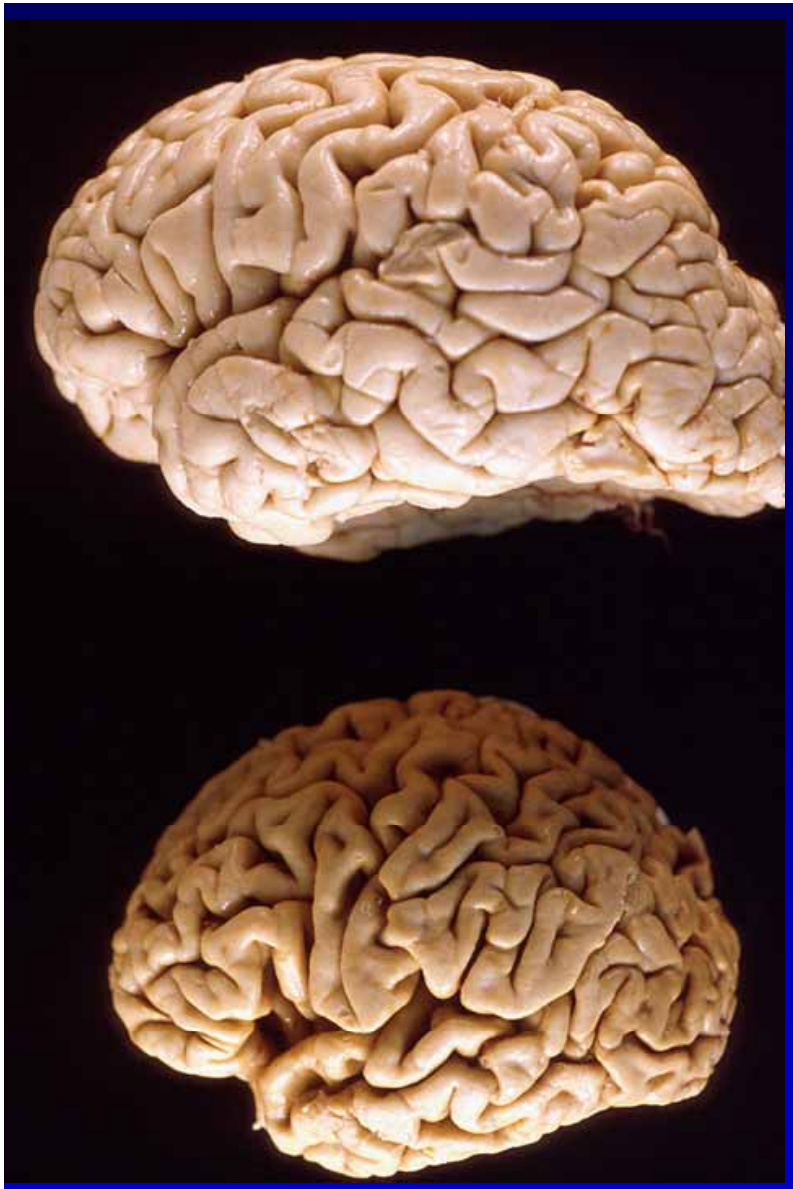
www.omsi.edu/visit/life/aging/brainText.cfm

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

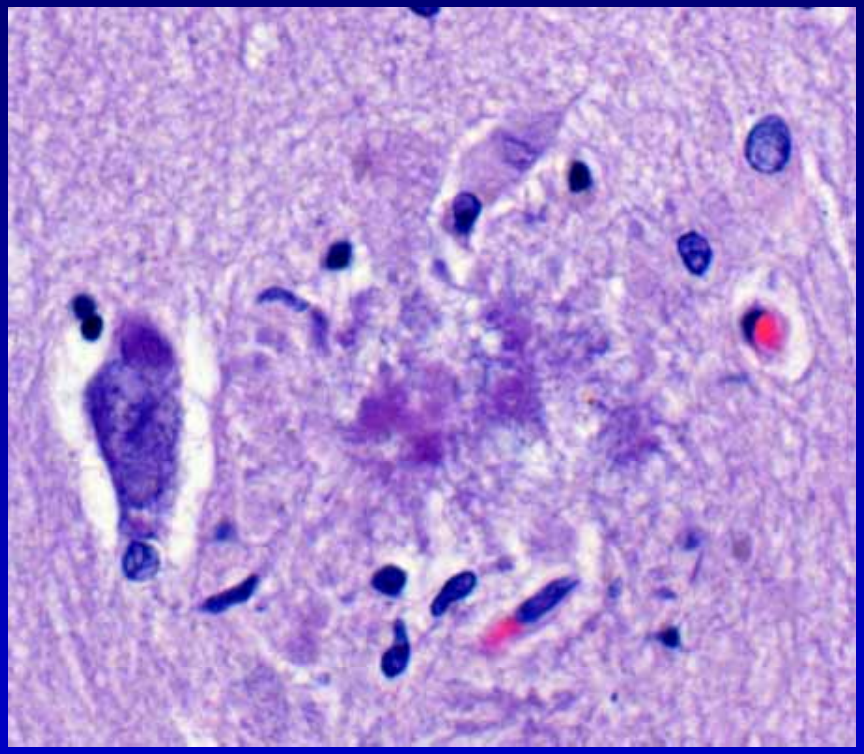
Alzheimer’s Disease: Gross Pathology

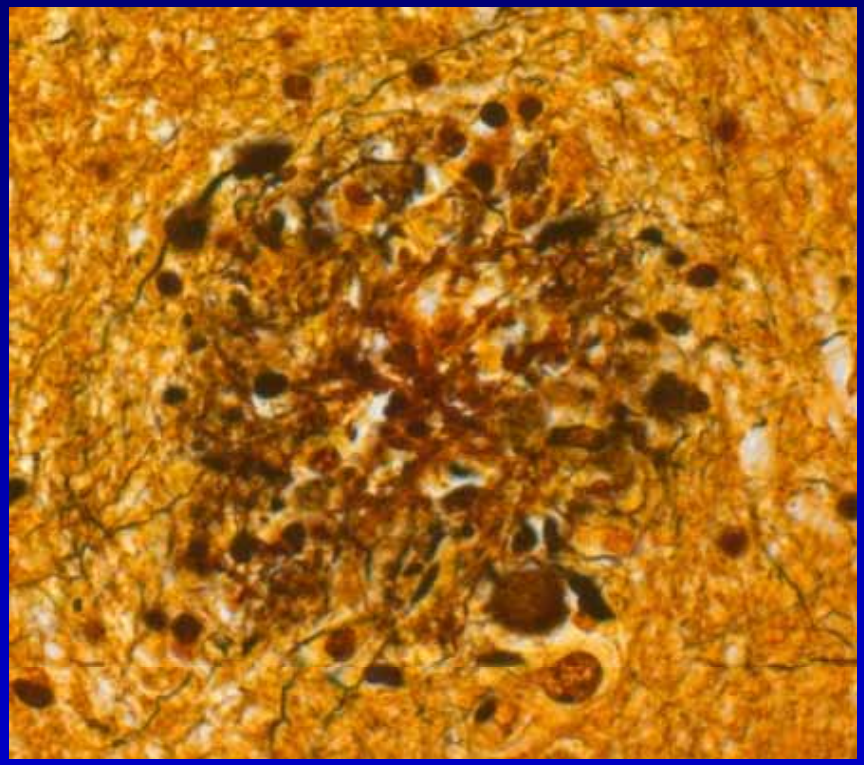


Alzheimer's disease demonstrating significant cortical atrophy. Note the widening of the sulci and the narrowing of the gyri.

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)

Alzheimer's Disease: Micropathology





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

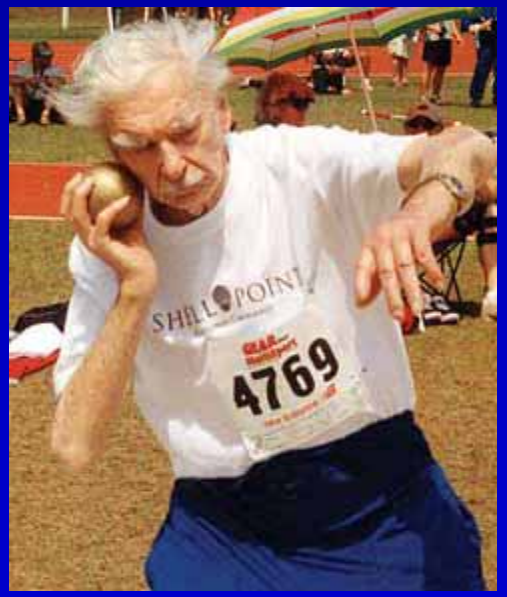
Marketed Benefits

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

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

Burt Morrow

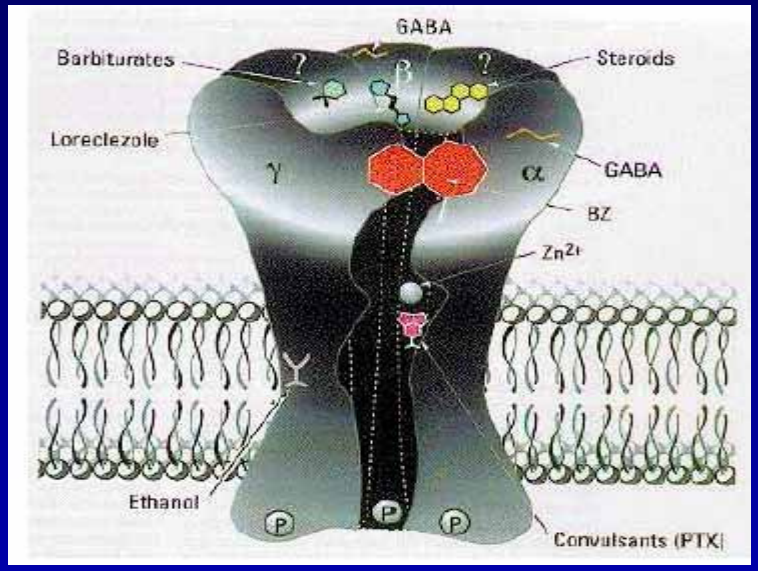
Lenore McDaniels



Everett Hosack

DHEA: Mechanism of Action

➢ Non-Genomic: Cell Surface



GABA-A Receptor

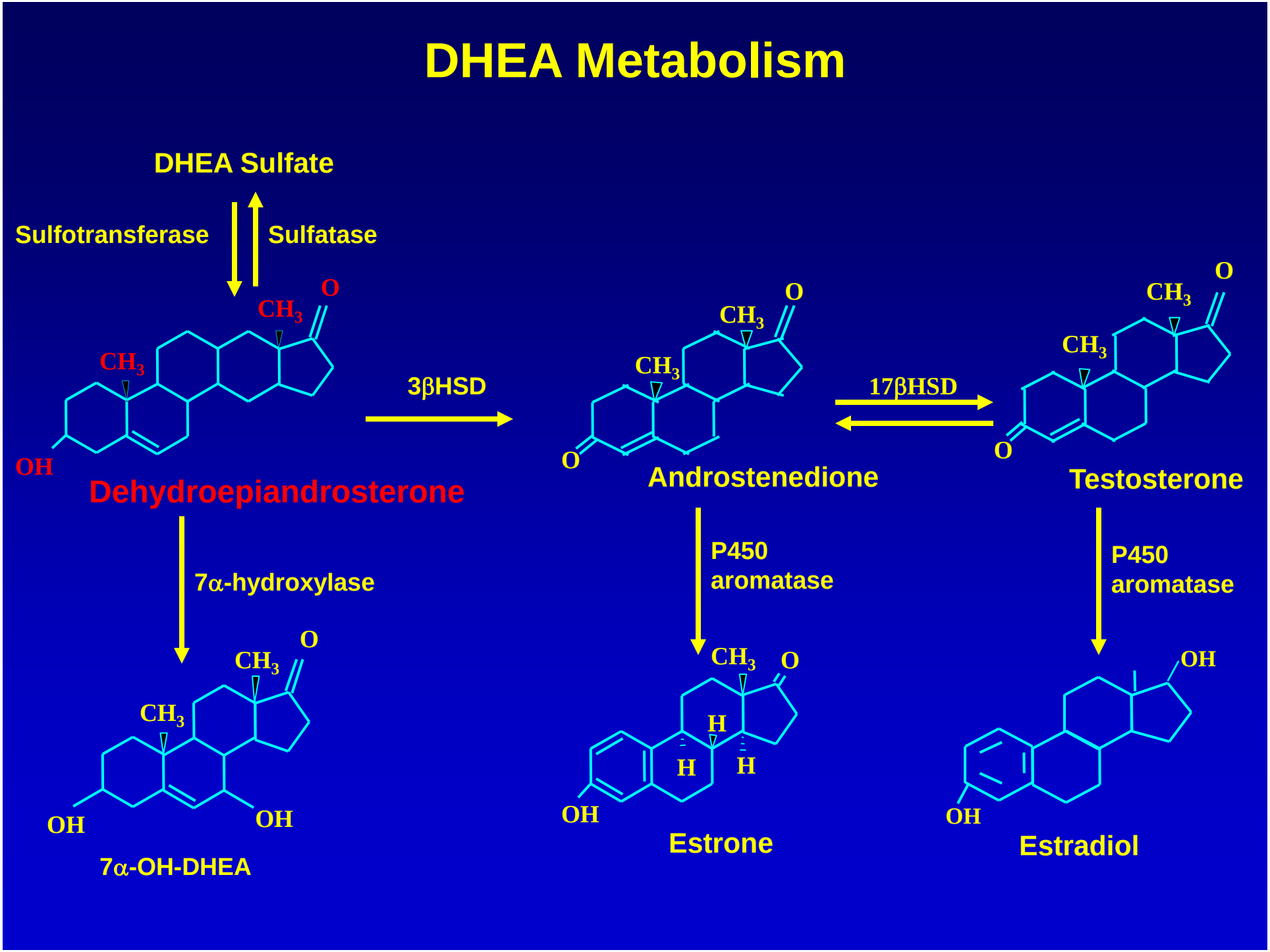
- Cl^- Channel
- Penatameric Structure: α, β, γ, δ, ε, ρ
- Regional heterogeneity in Structure
- Multiple Binding Sites
- Direct and Indirect Effects

➢ Genomic: Transcription

Androgen Receptor

- Intracellular Trafficking
- Transcriptional Activity
- Ligand Dependent

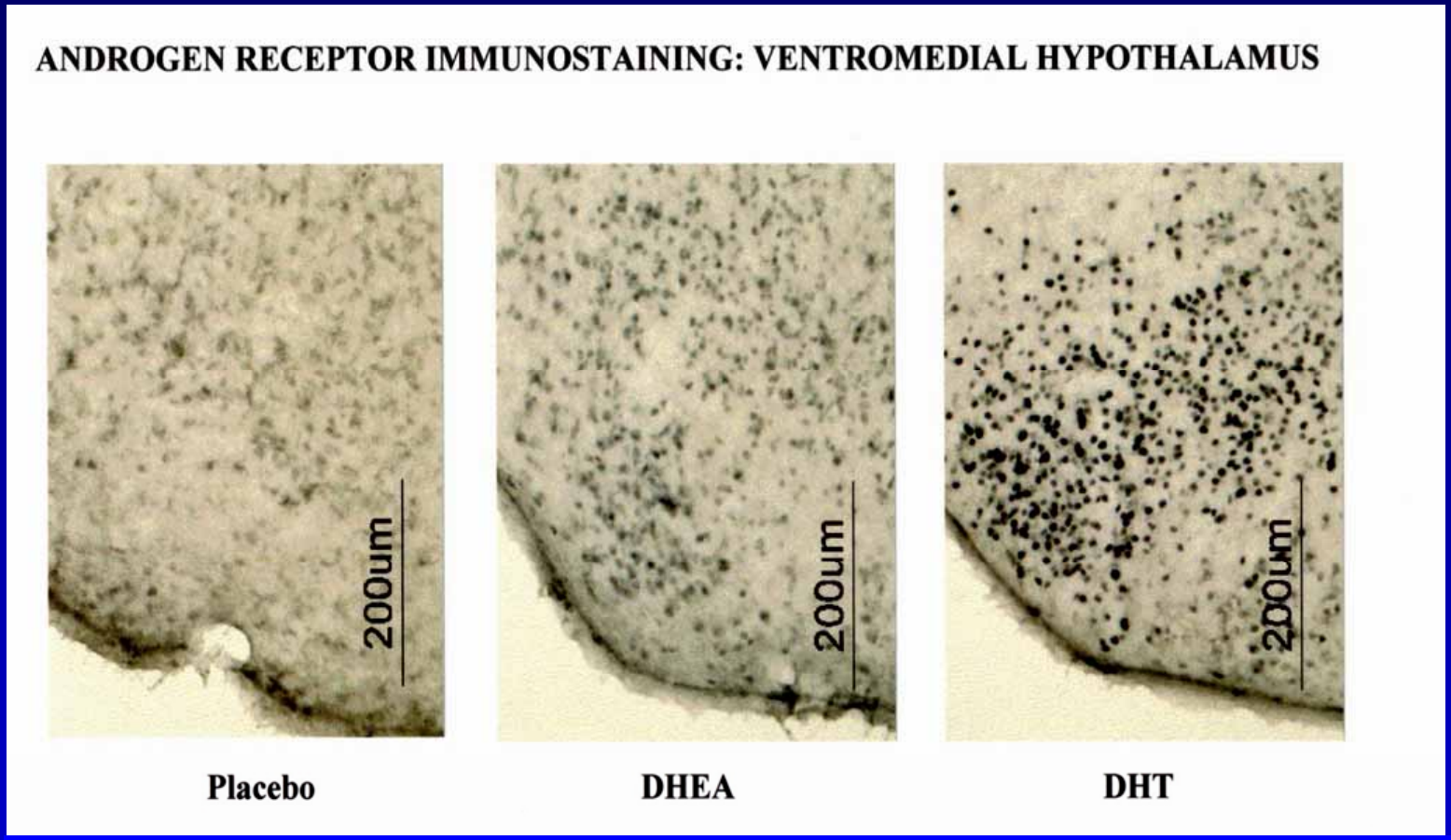
DHEA Metabolism



Functional Assays

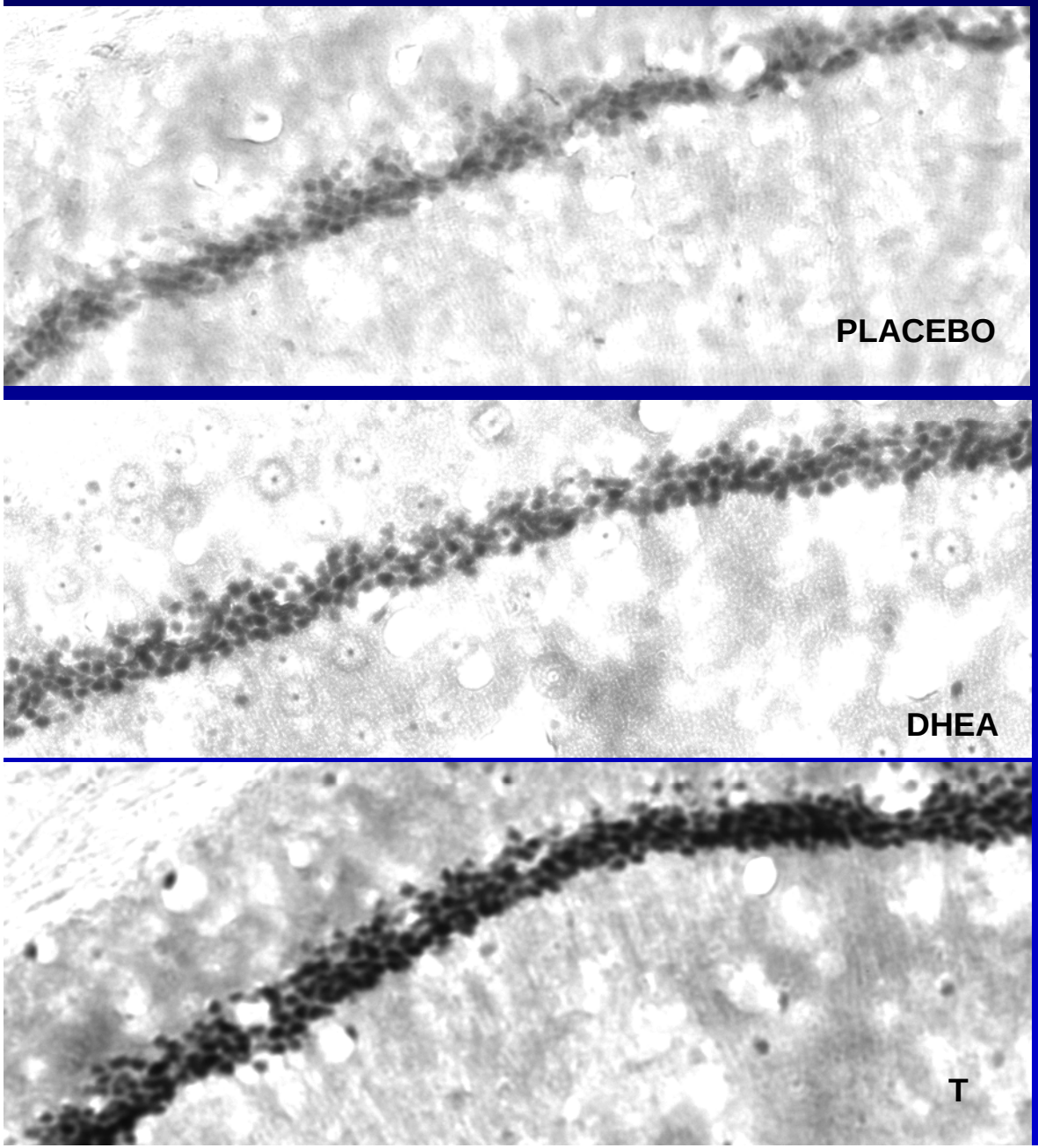
- Androgen Receptor: Immunochemistry
- AR Intracellular Trafficking: Confocal Microscopy
- DNA Microarray: Gene Regulation
- PCR: Microarray Validation

DHEA and DHT Upregulate AR in Female Mouse Brain



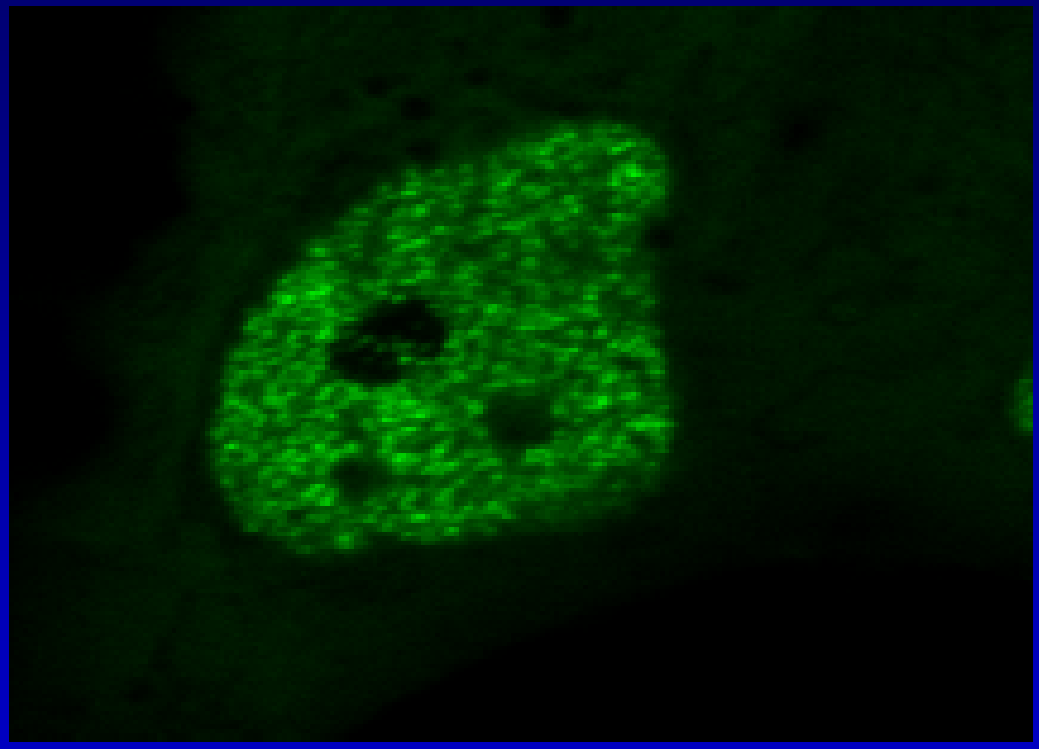
Ovariectomized female CF-1 mice were implanted with pellets containing DHEA (472 ug/day), DHT(72 ug/day), or placebo for 15 days. ICC for AR was conducted using PG-21 antibody according to methods in Lu et al.(1999).

DHEA and DHT Upregulate AR in Female Mouse Hippocampus

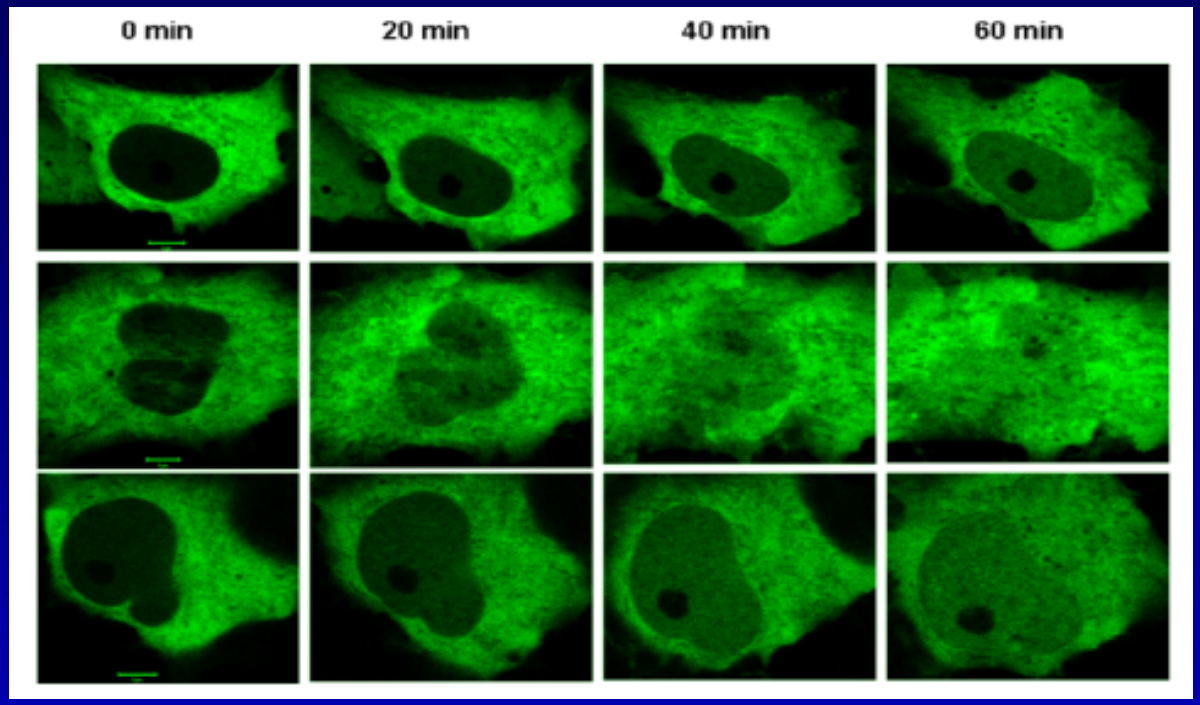


CF-1 female mice were ovariectomized and treated S.C. with DHEA (0.5 mg daily release), T (0.1mg daily release), or placebo pellet for seven days. AR immunoreactive cells are distributed only in the boundary of CA1 pyramidal cell layer.

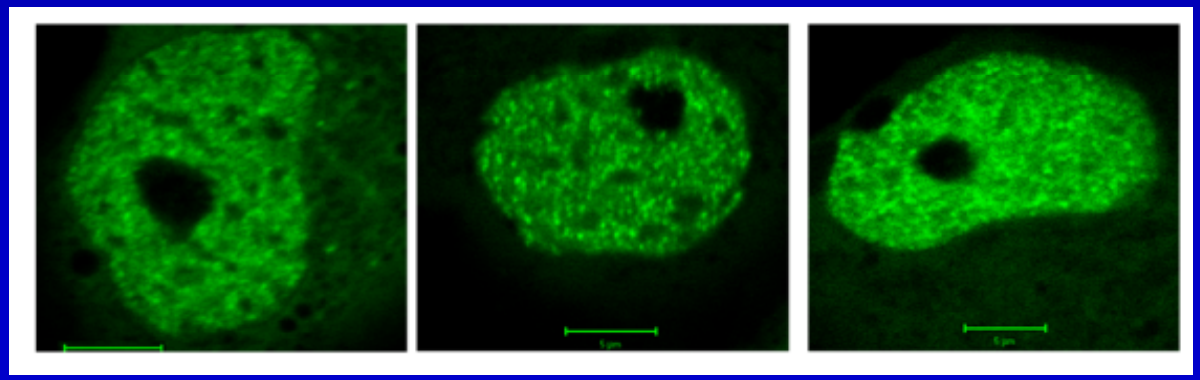
3. INTRACELLULAR TRAFFICKING



Intracellular Trafficking: Time Course



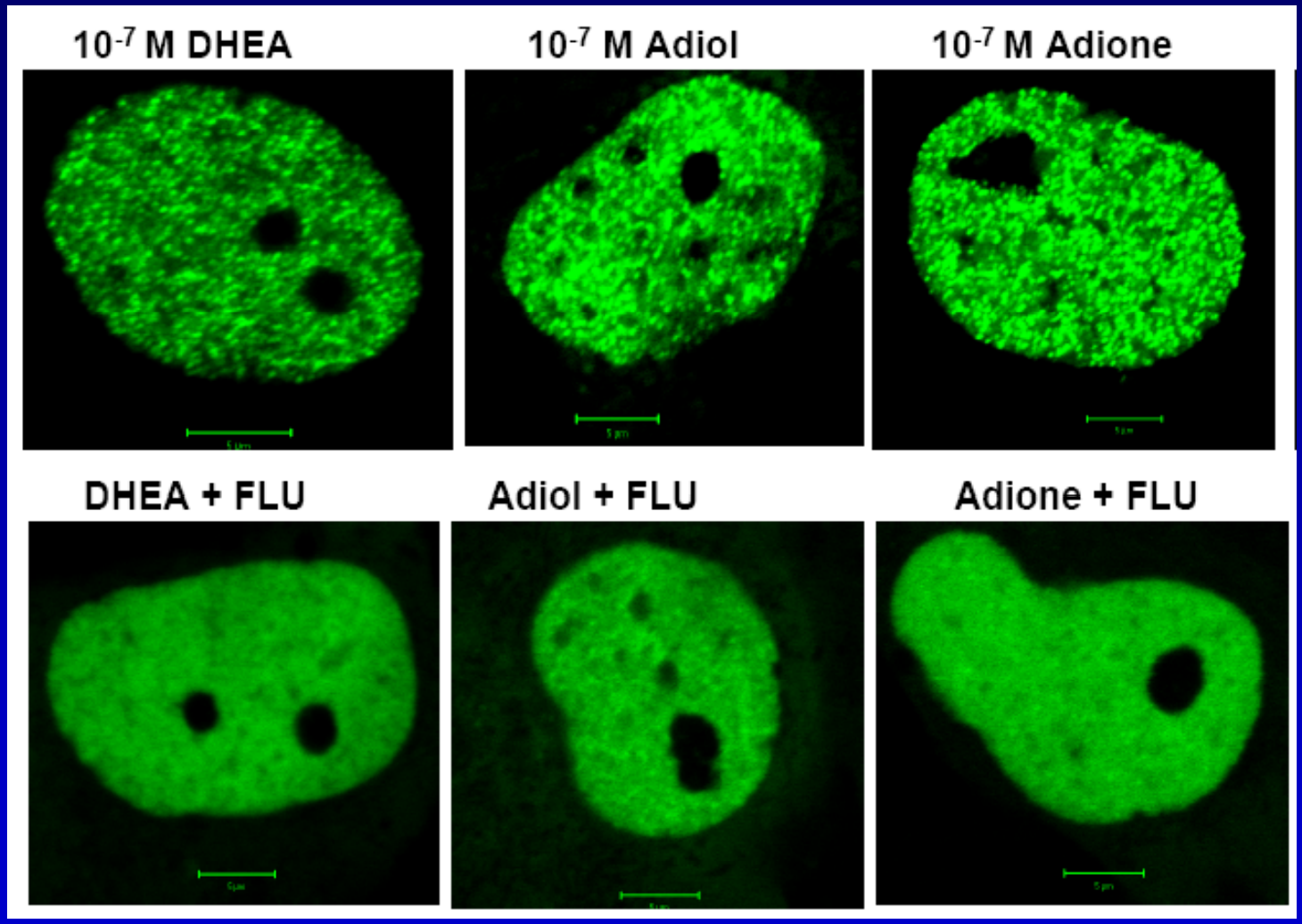
90 Minutes Post-treatment



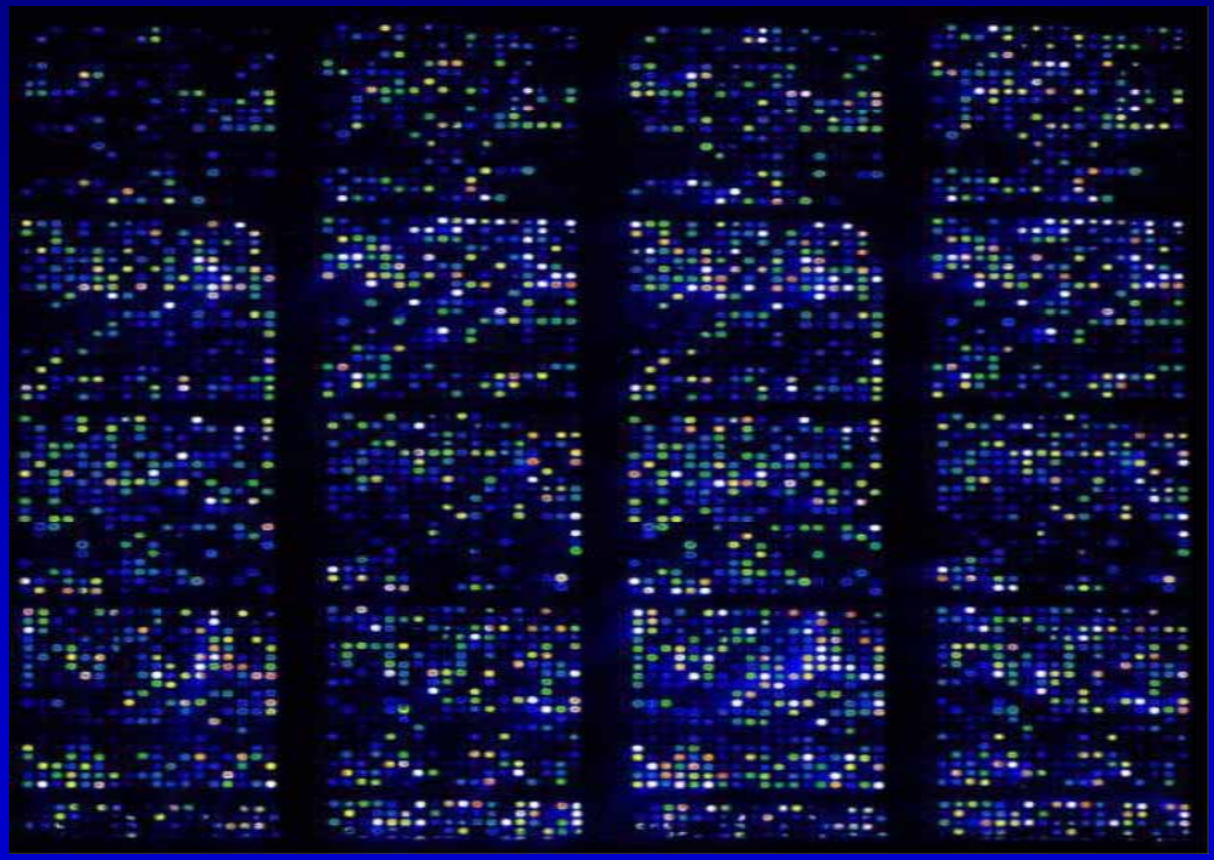
DHEA 10-5 **Adiol 10-6** **Adione 10-6**

Mo et al. (2006)

Nuclear Distribution of AR-GFP in COS-7 Cells Following Androgen or Androgen + Flutamide Treatment



Microarray Analysis



Genomic Analysis of DHEA- and DHT-Regulated Gene Expression in the Mouse Hypothalamus and Hippocampus

Experimental Design

Treatments

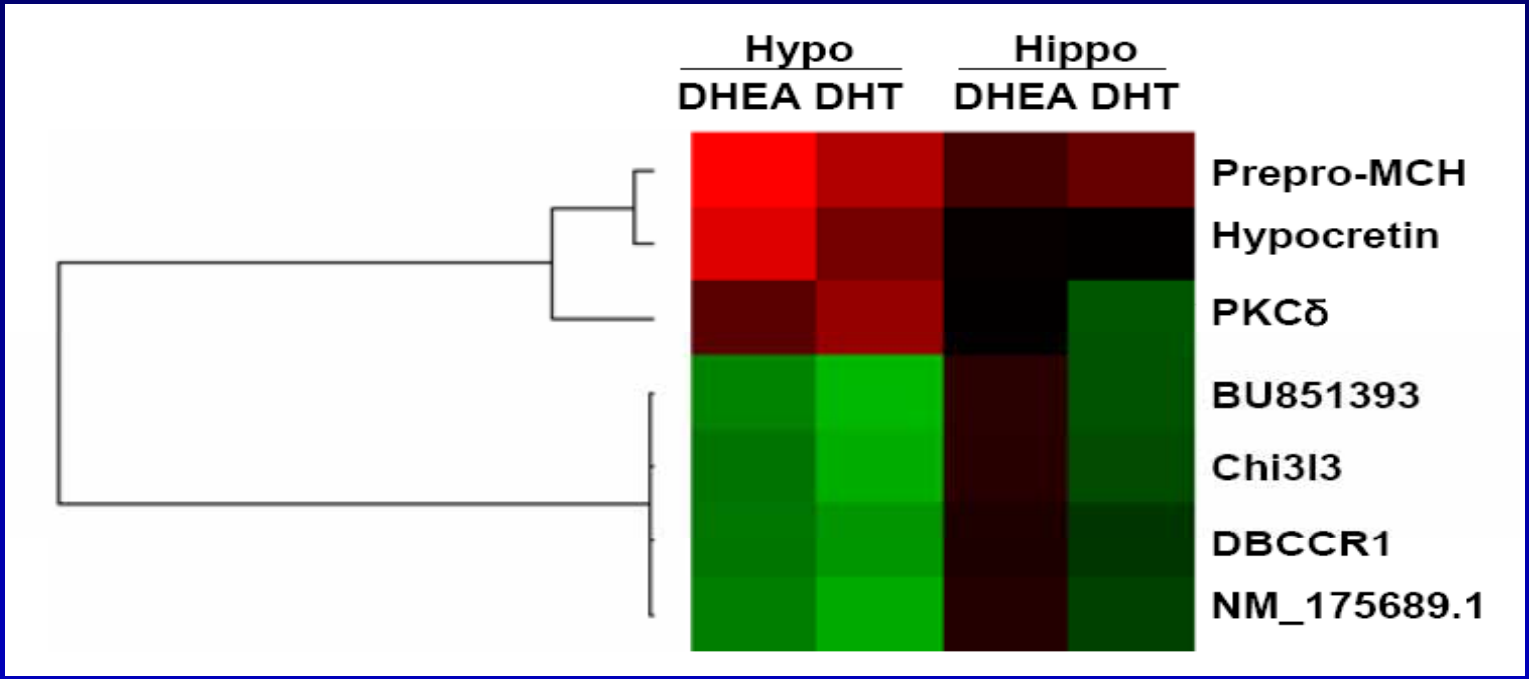
Control	DHEA	DHT
4 + 4 mice	4 + 4 mice	4 + 4 mice

Samples

	Control	DHEA	DHT
Hypothalamus	A1, A2	B1, B2	C1, C2
Hippocampus	D1, D2	E1, E2	F1, F2

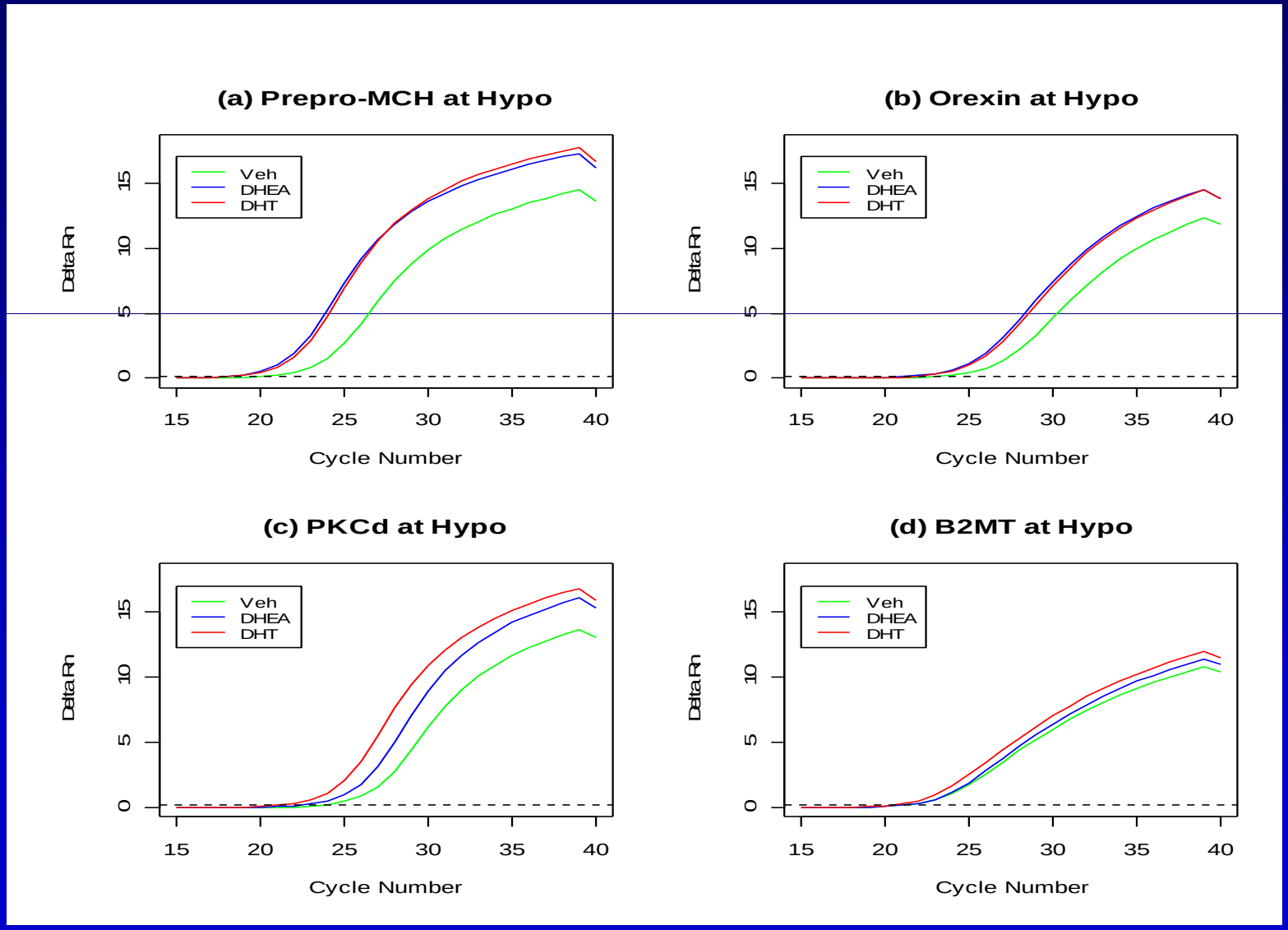
* Four brain regions were pooled to make one RNA samples

Heirarchical Cluster Analysis of Differentially Expressed Genes in Hypothalamus and Hippocampus



Gene Name	DHEA/Veh Hypothalamus	DHT/Veh Hypothalamus	DHEA/Veh Hippocampus	DHT/Veh Hippocampus
Prepro-MCH	3.50	2.02	1.30	1.50
Hypocretin	2.41	1.59	1.03	1.01
PKCδ	1.43	1.81	1.01	0.71

Real-time RT-PCR Analysis of Gene Expression in Mouse Hypothalamus



Summary

- 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

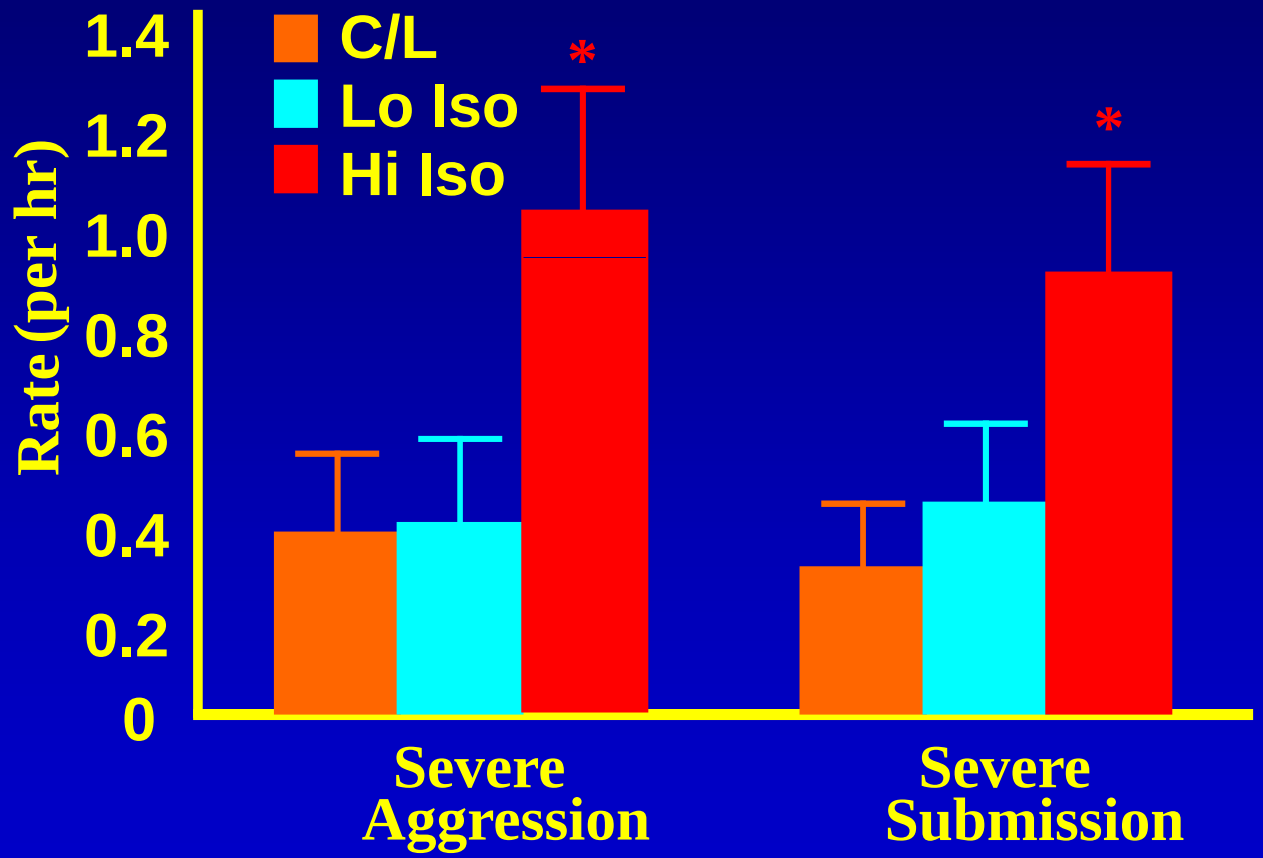
Soy & Resveratrol

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



SEVERE AGONISM
Bite
Charge
Grapple
Slap
Grab
Push

SEVERE SUBMISSION
Crouch
Flee
Scream

* p < 0.05 relative to C/L group.

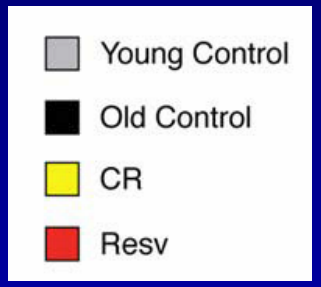
Simon, N. et al. 2004

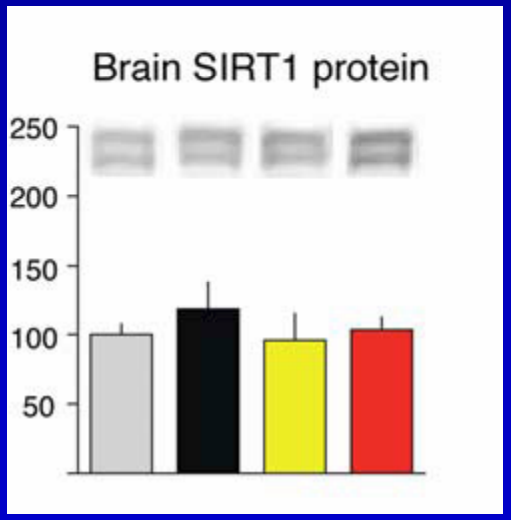
Resveratrol & Aging

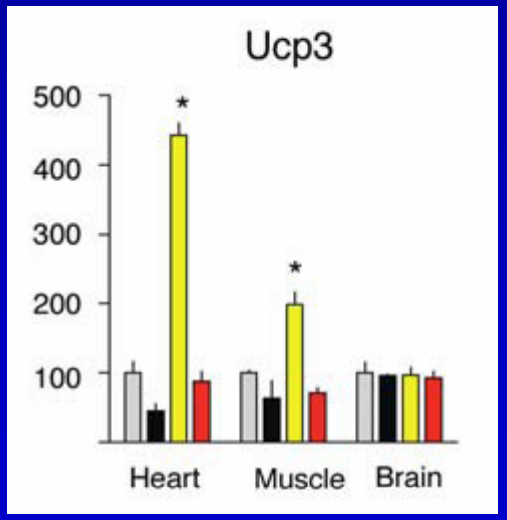
- Flavinoid produced by grapes and some berries
- Might help explain the “French Paradox”
- Increased the lifespan of yeast, worms, fruit flies, fish, and mice fed high-calorie diets
- Chemical structure is very similar to diethylstilbestrol
- Target enzymes linked to aging process “sirtuins”

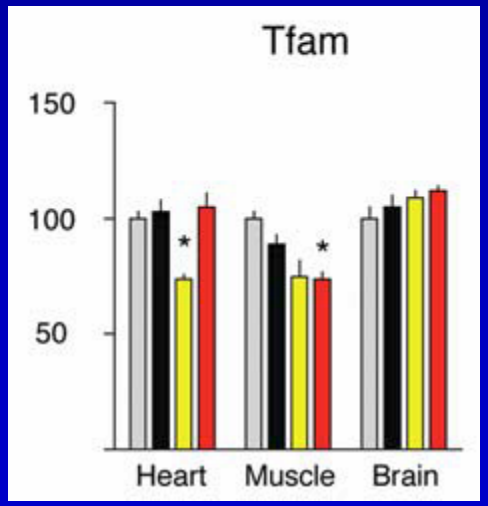
Resveratrol, Calorie Restriction, and Gene Expression

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.









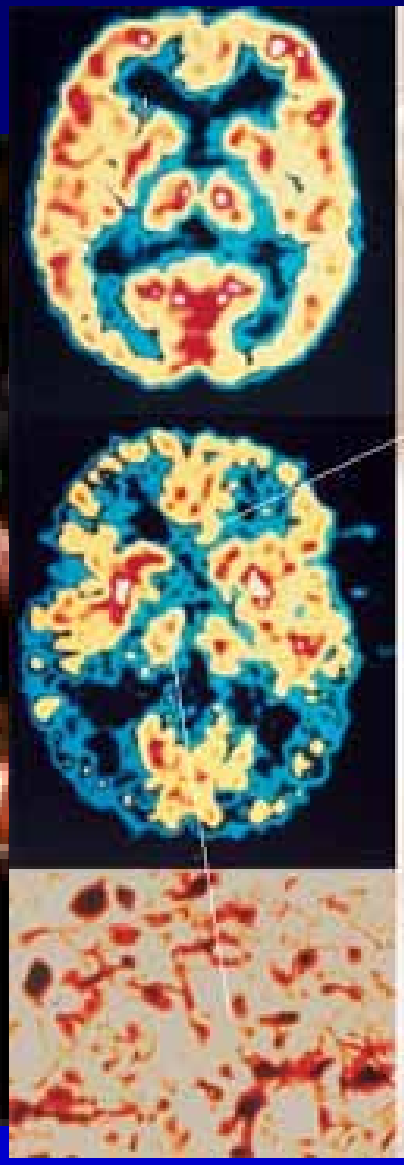
Barger et al (2009)

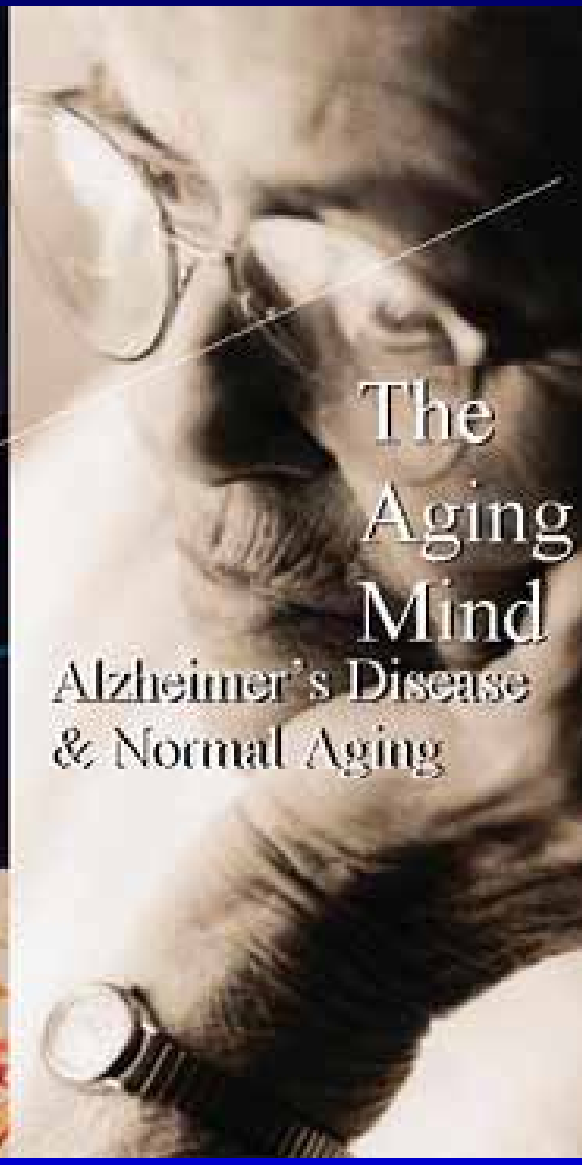
Summary

- 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 My generation The Zimmers 2:00 – The Who
- http://www.youtube.com/watch?v=594WLzzb3JI = The Who 37 secs (1965) – The Zimmers

- http://www.youtube.com/watch?v=PUnUv5jos68 resveratrol – Barbara Walters interview