Nutrition and Aging

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What is Aging?
What are the mechanisms behind aging?
Can we manipulate the aging process?
Figure 4.1. Survival Curve for U.S. Females: 1901 and 1998

Note: Data for 1901 refer to White females.
Sources: U.S. Census Bureau, 1936; U.S. Centers for Disease Control, 2001.
Aging is the major risk factor for **ALL chronic diseases**
Manipulating Lifespan/Healthspan

% Survival vs % Optimal Health

ΔLifespan

ΔHealthspan
Lifespan Manipulation C57Bl6/NIA

Survival proportion

Time (weeks)

CR
AL
HF
Aging Intervention Program; Working Hypothesis

Extracellular Space

Metabolic Inputs

Growth Factors
Nutrients
Oxidative Stress

Bioenergetic Sensors

Master Regulators

Cytoplasm

Nucleus

Modulatory Function

Metabolic Homeostasis
Stress Resistance

Healthspan
Aging

Longevity

Transcription Factors Co-activators

NAD$^+/\text{NADH}$

AMP/ATP

AMPK
mTOR
SIRT1
AKT

PGC1-$\alpha$
P53
FOXO
NRF2

Cytos/NQO1
Resveratrol is a phytoalexin produced in response to stress (e.g. infection, heat, UV).

- Found in wine (0.2-5.8 mg/L wine).
- Cancer protection, inflammation and antioxidant.
- Resveratrol activates SIRT1 in vitro.
- It is similar to caloric restriction in that there is much debate about its mechanism(s).

Resveratrol citations appearing on PubMed as a function of year.
Aging Intervention Mouse Program

Resveratrol 100 and 400 mg/kg

1 year old male C57Bl6/J

11 Groups, n≥50 mice/group

- Food Intake
- NMR Body Comp
- Serum/Urine Analysis
- Glucose Homeostasis
- Tissue Analysis
- Behavior
- Immune/Stress test
- Metabolic assessment

Healthspan
Lifespan

C57BL/6J
- Males
- Aged (1y)
- n ≥ 50/group
- Microchipped (ID+Temp transponders)
Lifespan data

Survival proportion

Time (weeks)

- Standard diet control
- SD high resv
- EOD low resv
- High calorie control
- HC high resv
Health and Lifespan Summary

- Protection against fatty liver induced by HF
- Increased insulin sensitivity
- Gene expression pattern similar to standard diet for HF mice and to CR for SD mice
- Increased performance on a rotarod
- Mean and maximum lifespan extension in 3 groups (HF+HR, HF+LR and EOD+LR)
- Reduction in cataracts
- Improve bone health parameters
- Reduced damage/stress in cardiovascular system
Resveratrol improves health and survival of mice on a high-calorie diet

November, 2006

ARTICLES

Resveratrol improves health and survival of mice on a high-calorie diet


Cell Metabolism

Short Article

Resveratrol Delays Age-Related Deterioration and Mimics Transcriptional Aspects of Dietary Restriction without Extending Life Span

Will Resveratrol Improve Cardiovascular Function In Monkeys on a High Fat Diet?

Resveratrol Non-Human Primate Work-in-progress!

Julie Mattison and Kevin Pearson
Nonhuman primates

- Resveratrol study
  - 24 Male rhesus monkeys (*Macaca mulatta*)
  - age range: 7-13 years (full adult)
  - body mass range: 7-20 kg
  - 24 month study
Groups and Timeline

Baseline Collection

24 monkeys
Standard Diet (SD)

Group A
10 HFS + Resv

42% kcal fat
27% kcal sucrose
40 mg RESV
twice daily

3 months

6 months

9 months

12 months

Increase RESV dose to 240 mg
twice daily

Group B
10 HFS

42% kcal fat
27% kcal sucrose
Placebo twice daily

Group C
4 SD control

13% kcal fat
<5% sucrose
Placebo twice daily

6 months

9 months

12 months

Increase RESV dose to 240 mg
twice daily

15 months

18 months

21 months

24 months

Sacrifice and tissue collection
Body Weight & Composition

Body Weight

Avg Weight (kg)

Baseline 1 yr 40 1 yr 240

Control HFS HFS + Resveratrol

LEAN:FAT

Baseline 1 yr 40 1 yr 240

HFS RESV
Pulse Wave Velocity

PWV = Distance (D) / Time delay (ΔT)
Pulse Wave Velocity
Pulse Wave Velocity

 PWV (cm/sec)

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* * *

* p<0.01
# p<0.05
Parametric Analysis of Gene Set Enrichment (PAGE)

Uses *a priori* defined groupings of genes into functional pathways

http://www.broad.mit.edu/gsea/msigdb/msigdb_index.html
Microarray analysis

Parametric analysis of gene set enrichment
Uses *a priori* defined groupings of genes into functional pathways

Resveratrol opposes the transcriptional effects of a high calorie diet in Rhesus Monkeys, all 24 monkeys were arrayed.
Monkey vs. Mice, Genes Reversed by Resveratrol

Heart

Fat

Muscle

APOD  EEF1B2
ARF3  EEF1G
ATF3  EIF4A1
ATP5B  GPX4
CEBPB  GSTM1
CRYAB  IGF1
CYP1B1  IL6ST
DNAJB6  MYL6
NDUFB8  NDUFA5
Preliminary Conclusions/Future Directions

- Resveratrol had a strong cardiovascular protective effect in NHP
- Improvement on PWV, an age related clinical marker of atherosclerosis
- Reversal of the gene transcription profiles in multiple tissues
- Overlap of genes/pathways in both species
- Studying mechanisms behind resveratrol’s effects
- Human Intervention study with Luigi Ferrucci at CRB
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“See, the problem with doing things to prolong your life is that all the extra years come at the end, when you’re old.”