The caloric restriction paradigm: implications for healthy human aging

Institute on Aging
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Rationale for caloric restriction research

(i) Aging itself is the most significant risk factor for a range of diseases including cancer, neurodegenerative disease, cardiovascular disease and diabetes.

(ii) Elucidation of the factors contributing to the aging process will identify novel targets for disease prevention and treatment.

Caloric restriction as a model of delayed aging is a research tool to determine the underlying causes of age-associated disease vulnerability.
Caloric restriction extends average and maximal lifespan in mice

C3B10RF1 female mice subject to early onset CR
Meta-analysis reveals conserved pathways responsive to caloric restriction

Barger et al in review
Transcriptional signature conserved with CR and genetic models of delayed aging
Transcriptional signature of health status
Insights from CR apply to health not just to aging
Mitochondrial function influences morbidity and survival

Dietary excess

Genetic defects

Chronological aging

Mitochondrial Dysfunction

Morbidity & mortality

Caloric restriction

Altered Mitochondrial Metabolism

Longevity
Inverse linear relationship between calorie intake and lifespan in mice

Nutrient sensitive metabolic regulators?
Aging, diet, and disease vulnerability, a central role for metabolic integrity

<table>
<thead>
<tr>
<th>Metabolic indicator</th>
<th>Amino acids</th>
<th>NAD</th>
<th>AMP</th>
<th>Fatty acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic regulator</td>
<td>mTOR</td>
<td>Siruins</td>
<td>AMPK</td>
<td>PPARs</td>
</tr>
</tbody>
</table>

| Aging          | ↓            | ↓    | ↑    | ↑            |
| Caloric restriction | ↑            | ↑    | ↓    | ↓            |
| Dietary excess | ?            | ↓    | ↑    | ↑            |
Metabolic reprogramming by CR

Hypothesis: CR induces a state of altered energy metabolism that underlies its ability to slow aging

Fundamental questions:

i) what are the mechanisms of CR, studies in mice, flies, worms, and yeast

ii) are CR insights translatable to human health, studies in NHPs

iii) can we identify CR mimetics, small molecule screens, pharmaceuticals nutraceuticals, ITP
Nonhuman primates have a lot to offer
Why the monkey model matters

Hudson et al 1996 Aging Clin. Exp. Res. 8:197

Table 3 - Body composition of adult Rhesus monkeys.

<table>
<thead>
<tr>
<th>AGE</th>
<th>N</th>
<th>LTM (kg)</th>
<th>FTM (kg)</th>
<th>% FTM</th>
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<tbody>
<tr>
<td>FEMALES</td>
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<tr>
<td>YA</td>
<td>7</td>
<td>5.05±0.11</td>
<td>0.95±0.44</td>
<td>13.3±5.3</td>
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<tr>
<td>MA</td>
<td>7</td>
<td>5.55±0.14</td>
<td>2.38±0.22</td>
<td>29.7±1.7</td>
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<tr>
<td>OA</td>
<td>7</td>
<td>4.50±0.31</td>
<td>1.75±0.45</td>
<td>18.5±4.7</td>
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<tr>
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<tr>
<td>YA</td>
<td>7</td>
<td>7.57±0.32</td>
<td>0.73±0.17</td>
<td>8.4±1.6</td>
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<tr>
<td>MA</td>
<td>7</td>
<td>7.56±0.35</td>
<td>1.24±0.41</td>
<td>18.0±4.1</td>
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<tr>
<td>OA</td>
<td>6</td>
<td>6.20±0.43</td>
<td>1.43±0.50</td>
<td>16.4±4.2</td>
</tr>
</tbody>
</table>

ANOVA p-values

Sex 0.001 NS 0.057
Age 0.001 0.009 0.007

Values are means ± SEM. Age: YA=6-9 years, MA=15-19 years, OA=26-30 years. LTM, FTM: lean and fat tissue body weight; BMC, BMD: bone mineral content and density, respectively. There were no significant interactions.

Table 2 - Indices of adiposity and tissue distribution.

<table>
<thead>
<tr>
<th>AGE</th>
<th>N</th>
<th>BMI (kg/m²)</th>
<th>BULGE (kg)</th>
<th>SAG (kg)</th>
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</thead>
<tbody>
<tr>
<td>FEMALES</td>
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<tr>
<td>YA</td>
<td>7</td>
<td>29.55±2.27</td>
<td>0.72±0.06</td>
<td>0.88±0.03</td>
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<tr>
<td>MA</td>
<td>7</td>
<td>36.54±1.23</td>
<td>0.90±0.01</td>
<td>0.96±0.02</td>
</tr>
<tr>
<td>OA</td>
<td>7</td>
<td>28.35±2.62</td>
<td>0.90±0.07</td>
<td>1.01±0.05</td>
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<tr>
<td>MALES</td>
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<tr>
<td>YA</td>
<td>7</td>
<td>32.59±0.92</td>
<td>0.65±0.01</td>
<td>0.81±0.02</td>
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<td>MA</td>
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<td>37.41±1.46</td>
<td>0.77±0.04</td>
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<tr>
<td>OA</td>
<td>6</td>
<td>33.50±3.40</td>
<td>0.86±0.07</td>
<td>0.97±0.04</td>
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</tbody>
</table>

ANOVA p-values

Sex NS NS 0.02
Age 0.007 0.001 0.0002

Values are means ± SEM. Age: YA=6-9 years, MA=15-19 years, OA=26-30 years. BMI: body mass index (BW/CR²). BULGE, SAG: ABCIR/CR and ABCIR/CHCIR, respectively. There were no significant age*sex interactions.
Adult onset CR lowers the incidence of age-related death in monkeys

Of the original 76 animals, 63% of the control animals died of age-related causes compared to 26% of the CR group (HR 2.4, p<0.001).

Colman et al  Nature Communications 5:3557 2014
CR delays the onset of age-related disease in monkeys.

Age-associated disease was detected at 3 times the rate in Control animals compared to CR animals.

Colman et al Science 325:201; 2009
CR reduces adiposity in a depot and gender specific manner

MRI detection of abdominal adiposity
CR prevents the age associated decline in physical activity

Longitudinal data

24 hour data

Metabolic chamber

CR prevents the age associated decline in physical activity and decreases the metabolic cost of movement.

CR enhances learning and execution in motor function tests

Fine Motor Performance During Different mMAP Tasks

Kastman et al J Neurosci 39:7940 2010
CR delays or prevents multiple age-related disease and disorders
Age induced changes in morphology and composition in skeletal muscle

middle age

Extreme old age

Phenotypes of sarcopenia
- Fiber loss
- Fiber atrophy
- Adiposity
- Inflammation
Metabolic imaging reveals impact of age on intracellular redox metabolism

Pugh et al Aging Cell 12:672 2013
Aging increases droplet size of intracellular lipid stores
The Fat’s where its At
WAT derived Systemic Signaling

- Adiponectin
- Multimeric Adiponectin
- AMPK
- PPARs
- FA utilization
- Lipokines

**WAT**

**Peripheral Tissue**
Adiposity and metabolic disease

Age and Weight Matched
Healthy
Normal insulin
Insulin sensitive

Impaired
Elevated insulin
Insulin resistant

2 years

Healthy and Prediagnosis

Percent body fat
ctrl Met\textsuperscript{i} \textit{pre-}D\textsubscript{x} vs. ctrl Met\textsuperscript{i} \textit{D}\textsubscript{x}

Abdominal circumference
ctrl Met\textsuperscript{i} \textit{pre-}D\textsubscript{x} vs. ctrl Met\textsuperscript{i} \textit{D}\textsubscript{x}

AdipoQ Total
ctrl Met\textsuperscript{i} \textit{pre-}D\textsubscript{x} vs. ctrl Met\textsuperscript{i} \textit{D}\textsubscript{x}

p=0.07

AdipoQ HMW
ctrl Met\textsuperscript{i} \textit{pre-}D\textsubscript{x} vs. ctrl Met\textsuperscript{i} \textit{D}\textsubscript{x}
Changes in lipid metabolism and onset of metabolic disease

Longitudinal transitions (concentration)

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Longitudinal transitions (percentage)

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Legend:

- □ p>0.10
- □ p<0.10
- □ p<0.05
- □ p<0.01

THE UNIVERSITY OF WISCONSIN MADISON
Lipid profiling reveals late and early effects in the progression to metabolic impairment.
Where and What really matter
CR protects against brain aging

Gray matter regions
• Putamen
• Insula
• Caudate

Cognitive & motor functions

Colman et al Science 325:201; 2009
Influence of insulin on GM

Motor & somatosensory

Hippocampus

Insulin’s effects are region
And diet specific

Willette et al Diabetes 61:1036 2012
Mitochondrial metabolism in the aging Hippocampus
Brain region specific changes in metabolism
Metabolic links to development and progression of neurodegenerative disease
Insights from CR apply to health not just to aging

Nonhuman primates have a lot to offer

The Fat’s where its At

Where and What really matter

CR research points to a key role for metabolism in aging & delayed aging
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