Dietary Protein and Healthy Aging: Controversies and Mechanisms

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States of Amino Acid Nutrition

- Toxicity
- Supplementation
- Adequacy
- Limitation
- Deprivation/depletion
- Devoid

Balanced

Imbalanced

Insufficient for growth; *but is this unhealthy?*
Dietary protein: obsession and controversy

Adapted from:
http://detox-fit.com/fighting-worlds-protein-obsession/
https://hpjmh.com/2011/03/14/where-do-you-get-your-protein/
https://thevegandatabase.com/incomplete-plant-proteins-myth/
Dietary restriction: do macronutrients matter?

Protein Leverage Hypothesis

<table>
<thead>
<tr>
<th>Balance of dietary macronutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low protein: High carbohydrate</td>
</tr>
<tr>
<td>↓ Circulating BCAA: glucose</td>
</tr>
<tr>
<td>↓ mTOR</td>
</tr>
<tr>
<td>↓ Insulin</td>
</tr>
<tr>
<td>↓ Glucose tolerance</td>
</tr>
<tr>
<td>↑ Mitochondrial activity</td>
</tr>
<tr>
<td>↑ Immune function</td>
</tr>
<tr>
<td>↑ Late-life cardiometabolic health</td>
</tr>
<tr>
<td>↑ Food intake</td>
</tr>
<tr>
<td>↑ Lifespan</td>
</tr>
<tr>
<td>↑ Obesity</td>
</tr>
</tbody>
</table>

Cell 161, March 26, 2015

doi: 10.3390/nu8060370
Dietary Paradigms for Metabolic Health and Longevity

- Calorie restriction
- Protein restriction
- Less animal protein, replace with plant protein
- Essential amino acid restriction
- Sulfur amino acid restriction

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Diet?

- Psychological & emotional
- Sociological (engaging with life & spirituality)
- Genetic
- Physiological (disease & impairment)

Successful Aging

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*Ageing Research Reviews 39 (2017) 78–86*

Sulfur Amino Acid Restriction (SAAR) extends lifespan and is associated with a lean, metabolically younger phenotype.


Sulfur Amino Acid Restriction: Mechanisms

- Food intake
- EE/Heat
- BW, % Body Fat
- % Lean Mass
- Glucose metabolism
- Lifespan 30-40%
- SNS outflow
- Thyroid function
- FAO
- Insulin sensitivity
de novo lipogenesis, TCA
- Uncoupled respiration
- FGF21
- Adiponectin
- Glucose
- Insulin sensitivity
- Leptin sensitivity
- Energy expenditure
- Body weight
- HPT Axis
- T4, T3
- DIO2, TRα1
- Gut microbiota
- FGF21
What’s so special about SAAR?

- SAAR has stronger metabolic effects versus leucine restriction (LR).

<table>
<thead>
<tr>
<th>Measured after 8 wk:</th>
<th>SAAR</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food intake</td>
<td>↑↑ (+38%)</td>
<td>↑ (+22%)</td>
</tr>
<tr>
<td>Body weight</td>
<td>↓↓ (-25%)</td>
<td>↓ (-16%)</td>
</tr>
<tr>
<td>% body fat mass</td>
<td>↓↓ (-30%)</td>
<td>↓ (-22%)</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>↓↓ (-81%)</td>
<td>↓ (-48%)</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Glucose clearance</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Circulating FGF21</td>
<td>↑↑↑</td>
<td>↔</td>
</tr>
<tr>
<td>Liver triglyceride content</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Liver lipogenic genes</td>
<td>↓</td>
<td>↔</td>
</tr>
</tbody>
</table>

Potential ways sulfur amino acid restriction improves health span

Antioxidant defenses, mitochondrial function

methylation histones/DNA
phospholipids
neurotransmitters
creatine synthesis

↑ antioxidant defenses, mitochondrial function

Adapted from: https://www.researchgate.net/publication/276164612_Thiol_redox_homeostasis_in_neurodegenerative_disease/figures?lo=1
Proposed Mechanisms for how Dietary Restriction Promotes Healthspan

Adapted from: Mirzaei et al., 2014
Integrated Stress Response

**ISR Functions**
- Adaptation
- Hormesis
- Preconditioning

**Diet**
- Vegetables

**Drugs**
- Asparaginase Epar
- Vial with medication

**Genetics**
- DNA helix

**EMBO Reports (2016) 17: 1374–1395**
The ISR Meets the UPR at the ER

- **ISR**
  - GCN2
  - eIF2(P)
  - ATF4
  - mTORC1
  - Autophagy

- **UPR**
  - S1P, S2P
  - MEK
  - ERK
  - JNK(P)
  - IRE1
  - cATF6
  - ATF6

- **Gene Transcription**
  - Gene expression changes
  - Redox status, metabolism, autophagy, cell fate
  - ERAD, chaperones, folding

- **Lysosome**
  - ↓ mTORC1

- **ER**
  - Nucleus
Potential Areas for Collaboration:

Mechanisms linking dietary restriction with aging biology.
- Nutrient sensing pathways (ISR, mTOR)
- Proteostasis control (UPR, autophagy)
- Environmental factors (temperature, light, physical activity/exercise as medicine)
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Nicholas Margolies, MS
Emily T. Mirek, BS
Inna A. Nikonorova, PhD
Ashley P. Pettit, PhD

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Thank you! Questions?

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