
“The Brain, Energy Metabolism and Hormetic Pathways to Optimal Health”

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Synaptic Plasticity
Neuron Survival

![Graph showing the relationship between glutamate concentration and neuron survival.](image1)

Adaptive Response (Hormesis)

Toxicity

Glutamate Concentration


Stem Cells

OUTPUT
(Improved Cognition, Mood, Neuromuscular Performance)

INPUT
(Mild Intermittent Stressors)
Energy Restriction
Exercise
Intellectual Enrichment
Phytochemicals / drugs

CA1

CA2

CA3

Dentate Gyrus

Neurogenic Niche

BF2

BDNF

OUTPUT
(Improved Cognition, Mood, Neuromuscular Performance)

INPUT
(Mild Intermittent Stressors)
Energy Restriction
Exercise
Intellectual Enrichment
Phytochemicals / drugs
Henriette Van Praag
Running enhances spatial pattern separation in mice
Energy Restriction

Mild Cellular Stress
(Energy, Calcium, ROS)
TF activation

TF activation

BDNF
Chaperones
UCPs
Mn-SOD
PMRS
APE1
PGC-1α

ADAPTIVE RESPONSES

Glucose Metabolism
Autonomic Function

Phytochemicals and Drugs

Cognitive Enrichment

Exercise

Adverse Stressors and Disease

Neuroprotection
Neurogenesis
Synaptic plasticity
Neural network function

Reduced Oxidative Stress
Improved Cellular Energy Metabolism
Reduced Inflammation
Reduced DNA Damage

Resistance to Neurodegenerative Disorders

Resistance to Diabetes and Cardiovascular Disease
Summermatter and Handschin, 2012

Diagram showing the effects of exercise on muscle tissue.
Intermittent fasting reduces resting heart rate and blood pressure, and increases heart rate variability in rats.
Brainstem BDNF reduces resting heart rate and increases heart rate variability in mice.
Autonomic Nervous System Dysfunction Precedes Motor Symptoms in PD.

Brainstem Pathology Precedes Substantia Nigra Pathology in PD.
(Braak et al.; 2004; Cell Tissue Research)
Dietary energy intake modifies brainstem autonomic dysfunction caused by mutant α-synuclein.

INTERMITTENT FASTING AND HEALTH: HUMAN STUDIES


A TRIAL OF INTERMITTENT ENERGY RESTRICTION IN SUBJECTS AT RISK FOR COGNITIVE IMPAIRMENT. Mattson, Willette, Kapogianis et al.

Ages 55 – 70. Overweight and insulin resistant.
Cognitive testing – executive function
Structural and functional MRI
MRS spectroscopy
Cerebrospinal fluid – BDNF, Ab, pTau, markers of oxidative stress and inflammation
Plasma energy-regulating hormones and various markers of interest
ANS function – heart rate variability
AN ENERGY-CENTRIC VIEW OF A DAY IN THE LIVES OF OUR ANCESTORS AND OURSELVES

- Walking / running route
- Low energy density food
- High energy density food
- Predators and other hazards
- Intra-species competition
- Intra-species cooperation
- Shelter / food storage
- Effort-sparing technologies

10,000 years ago

BMI: 19-24

Transition to endurance runner

5 million years ago

BMI: 19-24

Transition to agriculture

Today

BMI: >25

Transition to sedentary / overfed / obese phenotype
Lab Members
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Dietary supplementation with nicotinamide or ketone esters ameliorates behavioral deficits and amyloid pathology in a mouse model of Alzheimer’s disease (3xTgAD mice).


Dietary Supplementation with Ketone Esters (d-β-hydroxybutyrate and (R)-1,3- butanediol) Ameliorates Anxiety-Like Behavior in 3xTgAD Mice

Elevated Plus Maze

Open Arm

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<thead>
<tr>
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<th>Phase 1</th>
<th>Phase 2</th>
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<tbody>
<tr>
<td>CHO</td>
<td><img src="Graph1_CHO.png" alt="Graph" /></td>
<td><img src="Graph1_KET.png" alt="Graph" /></td>
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<tr>
<td>KET</td>
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Center + Closed Arm

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Kashiwaya et al., 2012
Dietary Supplementation with Ketone Esters (\(\text{d-}\beta\text{-hydroxybutyrate}\) and \(\text{(R)-1,3-\text{butanediol}}\)) Ameliorates Anxiety-Like Behavior in 3xTgAD Mice

Open Field

- **Total Distance (cm)**
  - Phase 1: CHO, KET
  - Phase 2: *CHO*

- **Total Ambulatory Time (s)**
  - Phase 1: CHO, KET
  - Phase 2: *KET*

- **Total Ambulatory Counts**
  - Phase 1: CHO, KET
  - Phase 2: *KET*

- **Center Distance (cm)**
  - Phase 1: CHO, KET
  - Phase 2: *CHO*

- **Center Ambulatory Time (s)**
  - Phase 1: CHO, KET
  - Phase 2: *KET*

- **Center Ambulatory Counts**
  - Phase 1: CHO, KET
  - Phase 2: *KET*

**CHO**

**KET**

Phase 2
Ketone ester-fed 3xTgAD mice exhibit stronger context-dependent fear response related to hippocampal memory and a more rapid extinction of amygdala-dependent tone-related conditioned fear compared to 3xTgAD mice fed the control diet.
DISPELLING THE DEMONS (epileptic seizures)

Romans: Fasting

Medical Education
- Emphasize prevention
- Courses on energy restriction and exercise

Physicians
- Pediatricians
- General practice
- Psychiatrists
- Disease specialists

Diagnosis and Treatment
- Prescriptions
  - Energy restriction plans
  - Exercise plans
- Rehabilitation Facilities
  - 3–4 week intervention
  - Intermittent ER
  - Daily Exercise
  - Monthly Follow-Up

BRAIN-WASTING FORCES
- Food Industry
- Pharmaceutical Industry
- Agriculture
- Effort-sparing technologies

Government
- Federal
- State
- Local

Biomedical Research
- NIH
- Foundations
- Others

Education
- Primary
- Secondary
- College

Families
- Parents lead by example

Media
- Internet
- Television
- Newspapers

The Fasting Cure

by

UPTON SINCLAIR

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IN the Cosmopolitan Magazine for May, 1910, and in the Contemporary Review (London) for April, 1910, I published an article dealing with my experiences in fasting. I have written a great many magazine articles, but never one which attracted so much attention as this. The
My object in publishing this book is two-fold: first, to have something to which I can refer people, so that I will not have to answer half a dozen "fasting letters" every day for the rest of my life; and second, in the hope of attracting sufficient attention to the subject to interest some scientific men in making a real investigation of it. To-day we know certain facts about what is called "auto-intoxication"; we know them because Metchnikoff, Pawlow and others have made a thorough-going inquiry into the subject. I believe that the subject of fasting is one of just as great importance. I have stated facts in this book about myself; and I have quoted many letters which are genuine and beyond dispute. The cures which they record are altogether without precedent, I think. The reader will find in the course of the book (page 63) a tabulation of the results of 277 cases of fasting. In this number of desperate cases, there were only about half a dozen definite and unexplained failures reported. Surely it cannot be that medical men and scientists will continue for much longer to close their eyes to facts of such vital significance as this.