Intermittent Energetic Challenges, Adaptive Responses and Health: Lessons from the Brain

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Stem Cells

Dentate Gyrus

BDNF

OUTPUT
(Improved Cognition, Mood, Neuromuscular Performance)

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

CA3

CA1

CA2

Neurogenic Niche

Stem Cells

FGF2

Dentate Gyrus

BDNF

BDNF
Running enhances spatial pattern separation in mice
The number of mitochondria and ATP levels increase in hippocampal neurons as they grow and form synapses.

PCGC-1α levels can be selectively reduced or increased in hippocampal neurons using genetically engineered adenoviruses.
**PCGC-1α plays a critical role in synapse formation in developing hippocampal neurons**

![Immunofluorescence images of neurons expressing GFP and MitoDsRed](image)

- GFP-Si-Con
- GFP-Si-PGC1α
- GFP-PGC1α
PCGC-1α plays a critical role in the maintenance of synapses in the adult hippocampus.
Brain-derived neurotrophic factor (BDNF) stimulates PGC-1α promoter activity by a CREB-mediated mechanism.
Enhancement of synapse formation by BDNF requires PCGC-1α
Energetic Challenges
(exercise, Intermittent fasting, cognitive stimulation)

Glucose, Lactate, MCT2

BDNF, trkB

Glutamate

Ca^{2+}

PI3K, Akt, ERK

Ca^{2+}, CaMK

mTOR

mRNA, protein synthesis

ETC, ATP, NAD

MnSOD

Mitochondrial biogenesis

PGC-1α

Synapse formation and maintenance
Learning and memory
Resistance to age-related dysfunction and degeneration
Excitatory activity in nerve cells results in calcium- and mitochondria-mediated oxidative DNA damage which is repaired rapidly as a result of calcium- and CREB-mediated induction of the expression of the DNA repair enzyme APE1.

BDNF increases levels of APE1 in cultured cerebral cortical neurons

Exercise increases BDNF levels, CREB activation and APE1 levels in mouse brain cells in vivo.
"Fasting is the greatest remedy-- the physician within."

Philippus Paracelsus, one of the three fathers of Western medicine
"A little starvation can really do more for the average sick man than can the best medicines and the best doctors."

Mark Twain

"Humans live on one-quarter of what they eat; on the other three-quarters lives their doctor."

Egyptian pyramid inscription, 3800 B.C.
EFFECTS OF INTERMITTENT FASTING ON THE BODY AND BRAIN THAT MAY THWART OBESITY AND CHRONIC DISEASES

**BRAIN**
- Improved cognitive function
- Increased neurotrophic factors
- Increased stress resistance
- Reduced inflammation

**HEART**
- Reduced resting heart rate
- Reduced blood pressure
- Increased stress resistance

**FAT CELLS**
- Lipolysis
- Reduced leptin
- Increased adiponectin
- Reduced inflammation

**LIVER**
- Increased insulin sensitivity
- Ketone body production
- Decreased IGF-1 levels

**BLOOD**
- Decreased insulin, IGF-1 and leptin
- Increased ketones, adiponectin and ghrelin

**MUSCLE**
- Increased insulin sensitivity
- Increased efficiency
- Reduced inflammation

**INTESTINES**
- Reduced energy uptake
- Reduced inflammation
- Reduces cell proliferation

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**IF Promotes Fat ‘Burning’ and the Production of Beneficial Ketones**
Evolutionary Perspective: Our hunter/gatherer ancestors would not have survived unless their brain was functioning at high level when they were hungry.
Food Restriction Reduces Brain Damage and Improves Behavioral Outcome Following Excitotoxic and Metabolic Insults
Annador J. Bruce-Keller, PhD,*† Gloria Umberger, BS, MPH,† Robert McFall, BS,* and Mark P. Mattson, PhD*†

Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice
Wenzhen Duan*, Zhihong Guo*, Haiyang Jiang*, Melvin Ware†, Xiao-Jiang Li§, and Mark P. Mattson*§*

Neurobiology of Disease 26 (2007) 212–220
Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer’s disease
Veerendra Kumar Madala Halagappa,a Zhihong Guo,a Michelle Pearson,a Yasuji Matsuoka,b Roy G. Cutler,a Frank M. LaFerla,c and Mark P. Mattson*a,*

ANN NEUROL 2010;67:41–52
Age and Energy Intake Interact to Modify Cell Stress Pathways and Stroke Outcome
Thiruma V. Arumugam,* PhD,1,2 Terry M. Phillips,* DSc,3 Aiwu Cheng, PhD,1 Christopher H. Morrell, PhD,4 Mark P. Mattson, PhD,1,5 and Ruijian Wan, PhD1

Neurobiology of Aging 34 (2013) 928–935
Dietary energy intake modifies brainstem autonomic dysfunction caused by mutant α-synuclein
Kathleen J. Griffioen,a, Sarah M. Rothman,a, Bruce Ladenheim,b, Ruijian Wan,a, Neil Vranis,a, Emmette Hutchison,a, Eitan Okun,a,c, Jean Lud Cadet,b, Mark P. Mattson*a,d,*
Triple-Transgenic Model of Alzheimer’s Disease with Plaques and Tangles: Intracellular Aβ and Synaptic Dysfunction

Salvatore Oddo,¹ Antonella Caccamo,¹,⁵ Jason D. Shepherd,¹,⁵ M. Paul Murphy,³ Todd E. Golde,³ Rakez Kayed,² Raju Metherate,¹ Mark P. Mattson,⁴ Yama Akbari,¹ and Frank M. LaFerla¹,*

[Diagram showing the process of generating mice with the triple-transgenic model]
Effect of 14 months dietary regimens on Escape latency in Triple-Transgenic Alzheimer's mice in MWM (Females)

Latency in Seconds

Day1  Day2  Day3  Day4  Day5  Day6  Day7  Day8  1DayP  2DayP

C57 Adlib
3TgAD Adlib
3TgAD CR
3TgAD IF

17 month old females

Effect of 14 months dietary regimens on Path length in Triple-Transgenic Alzheimer’s mice in MWM (Females)

Path length in Centimeters

Day1  Day2  Day3  Day4  Day5  Day6  Day7  Day8  1DayP  2DayP

C57 Adlib
3TgAD Adlib
3TgAD CR
3TgAD IF

17 month old females

AL – ad libitum
IF- intermittent (alternate day) fasting
CR – 30% daily calorie restriction

Halagappa VK et al (2007)
DISPELLING THE DEMONS (epileptic seizures)

Romans: Fasting

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

ADAPTIVE RESPONSES

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

Neuroprotection
Neurogenesis
Synaptic plasticity
Neural network function

Adverse Stressors and Disease

Exercise
Cognitive Enrichment
Phytochemicals and Drugs

Glucose Metabolism
Autonomic Function

Resistance to Neurodegenerative Disorders
Resistance to Diabetes and Cardiovascular Disease

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

Aging