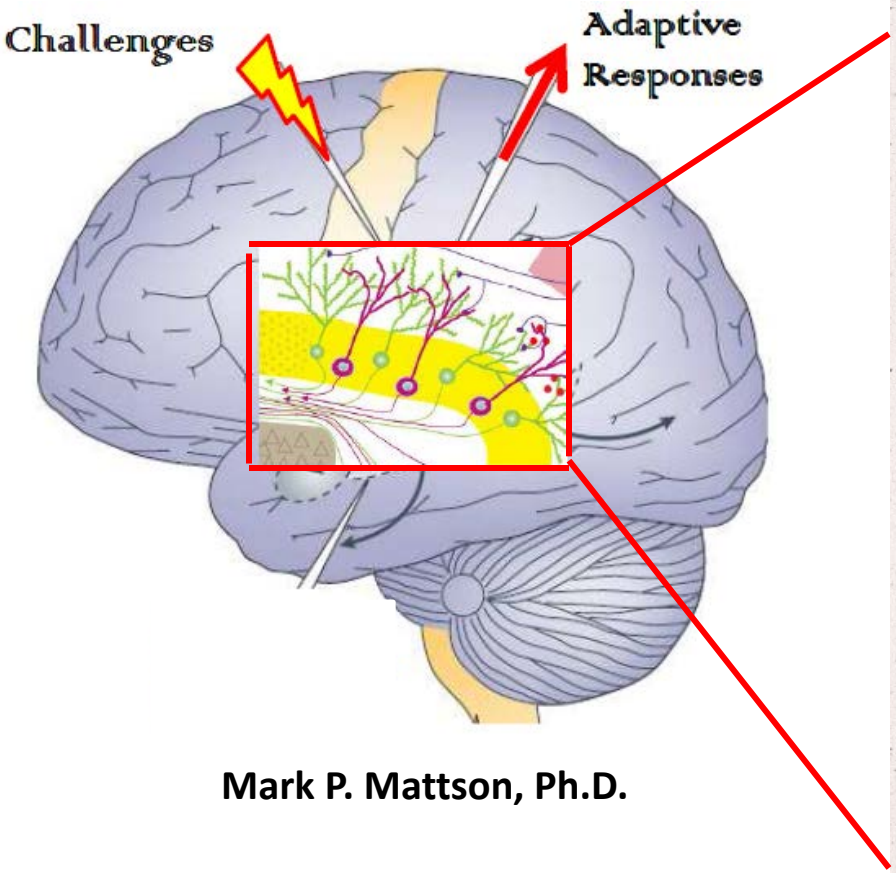
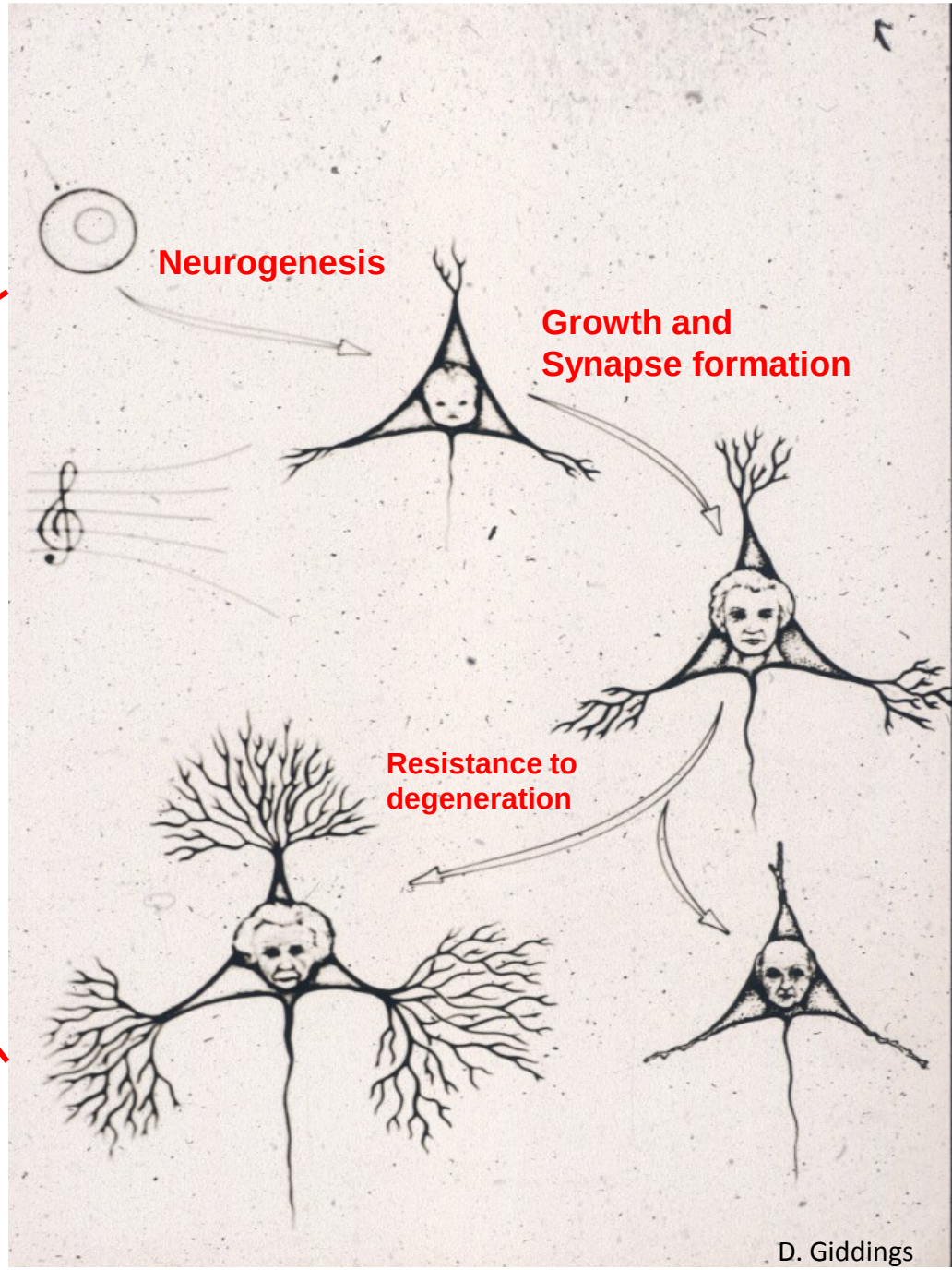
Intermittent Energetic Challenges, Adaptive Responses and Health: Lessons from the Brain



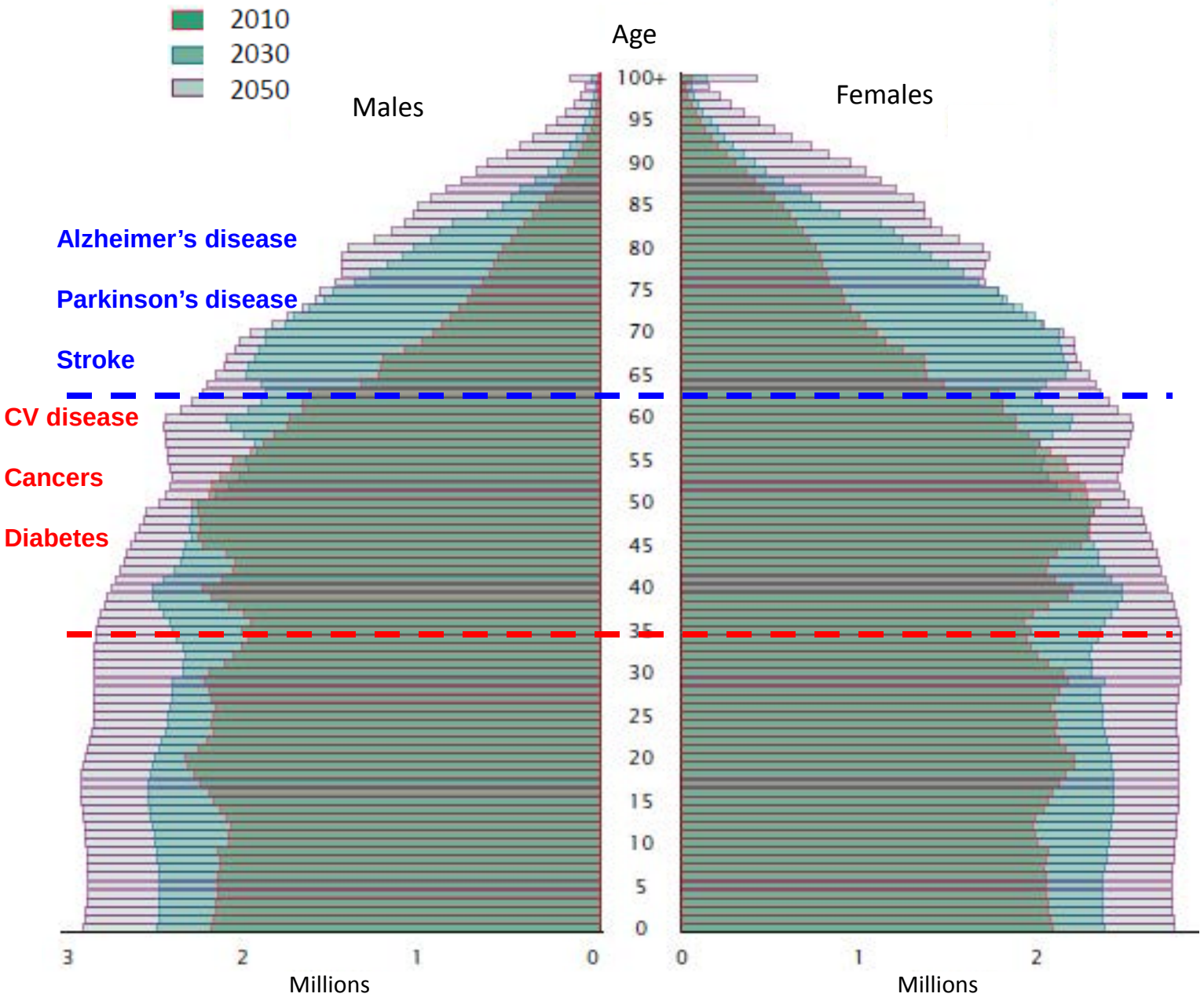
Mark P. Mattson, Ph.D.

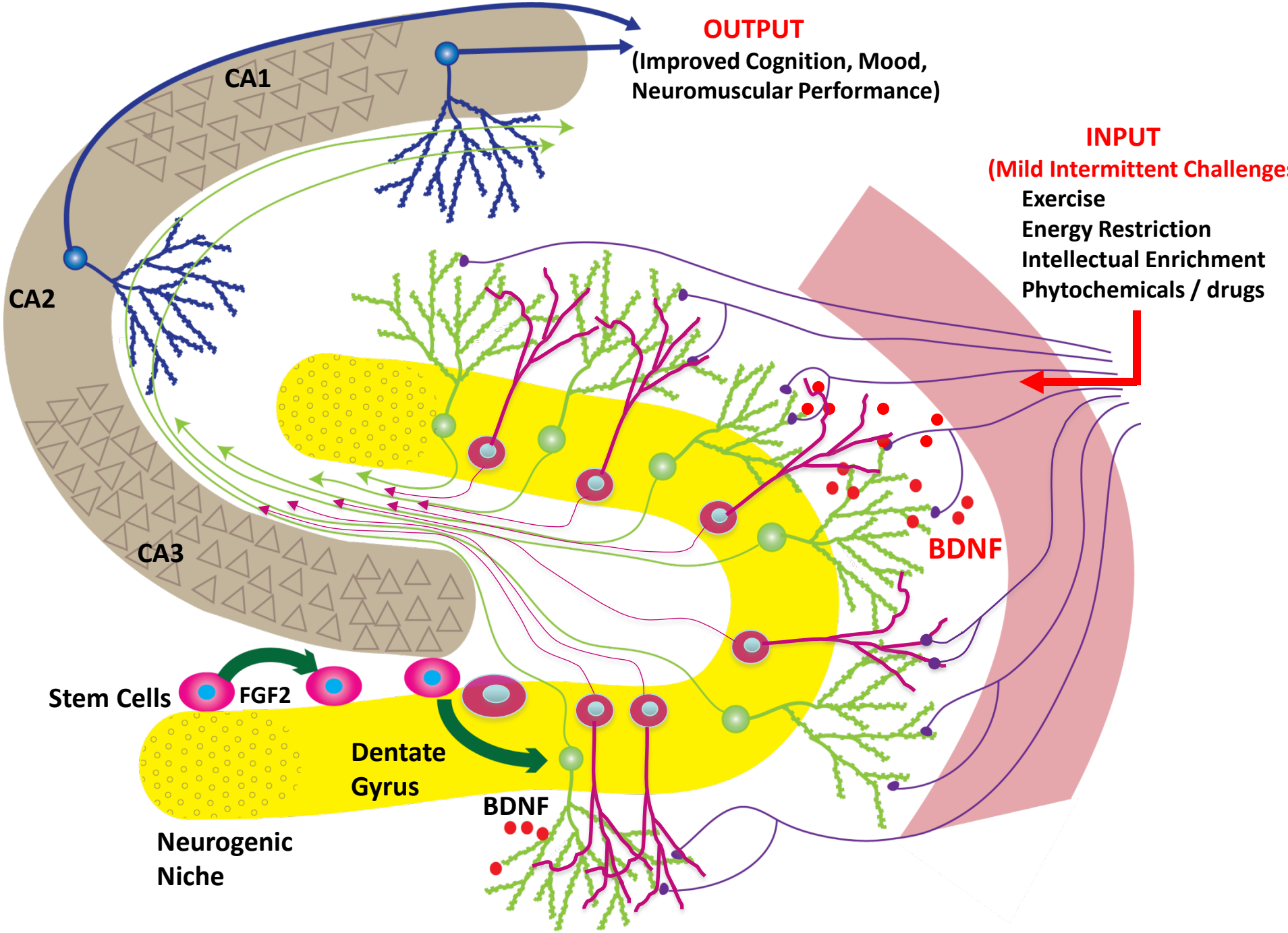
Chief, Laboratory of Neurosciences, National Institute on Aging IRP, Baltimore

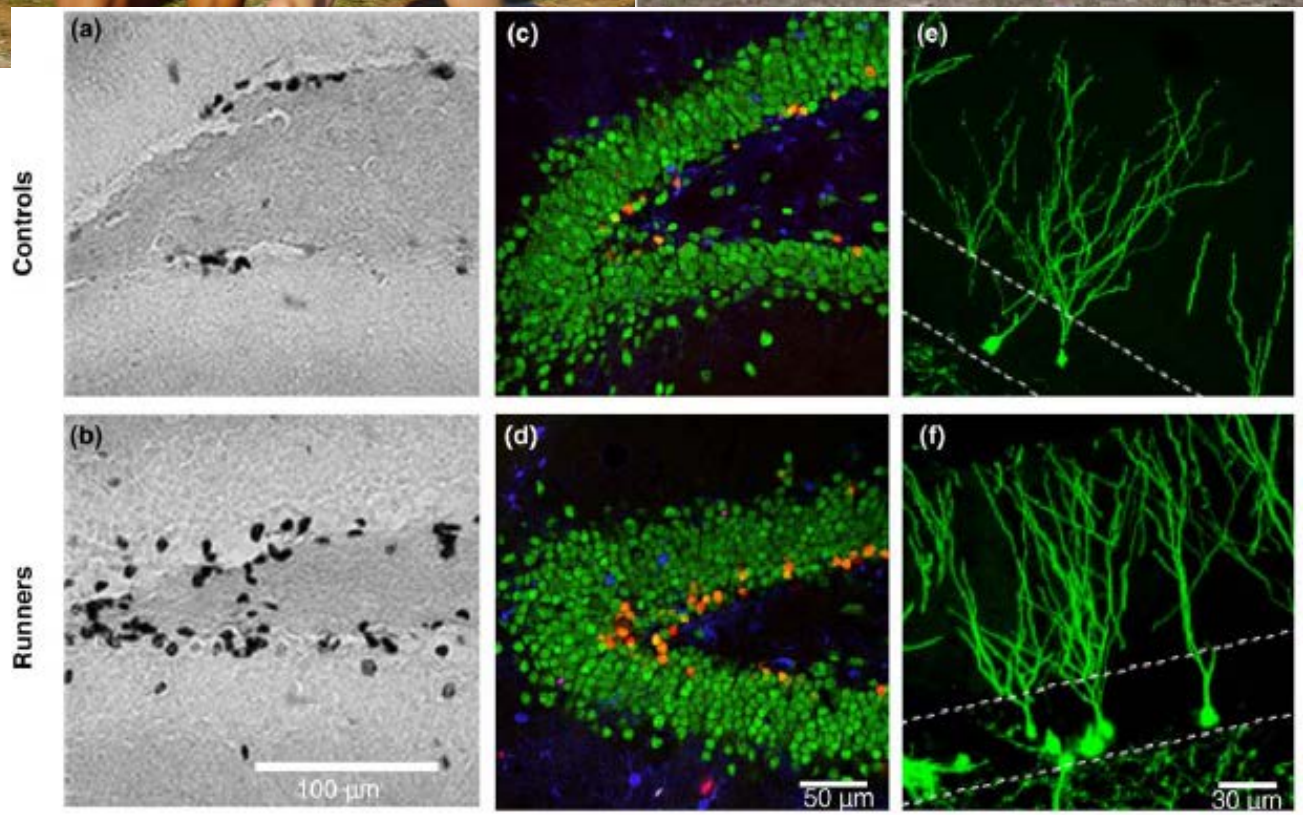
Professor, Department of Neuroscience, Johns Hopkins University School of Medicine



Age and Sex Structure of the US Population in 2010, 2030 and 2050



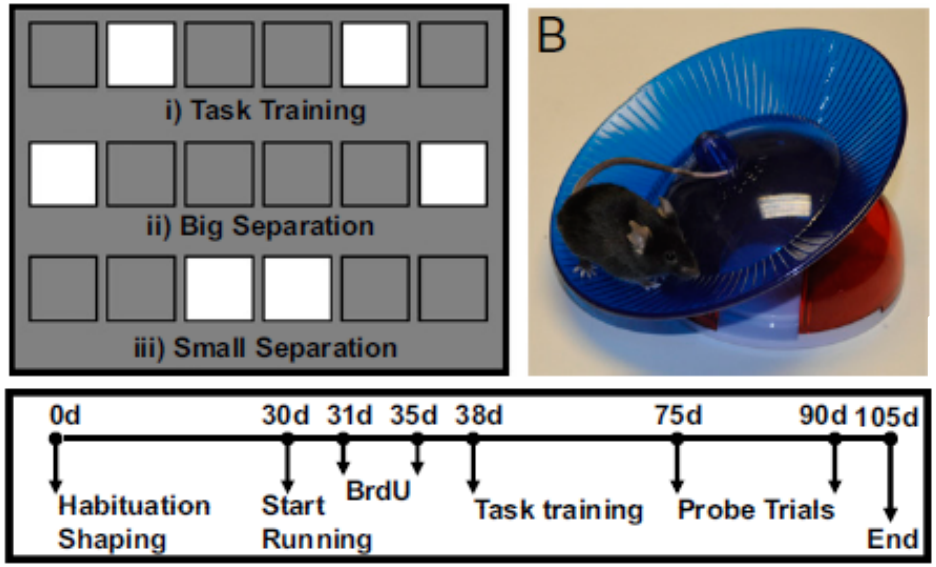

OUTPUT
(Improved Cognition, Mood,
Neuromuscular Performance)
INPUT
(Mild Intermittent Challenges
Exercise
Energy Restriction
Intellectual Enrichment
Phytochemicals / drugs
CA1
CA2
CA3
BDNF
Stem Cells
FGF2
Dentate
Gyrus
BDNF
Neurogenic
Niche

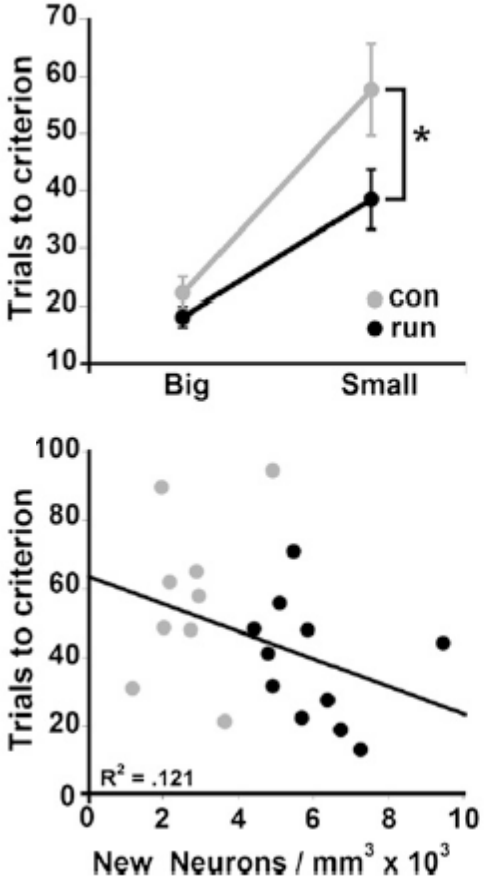


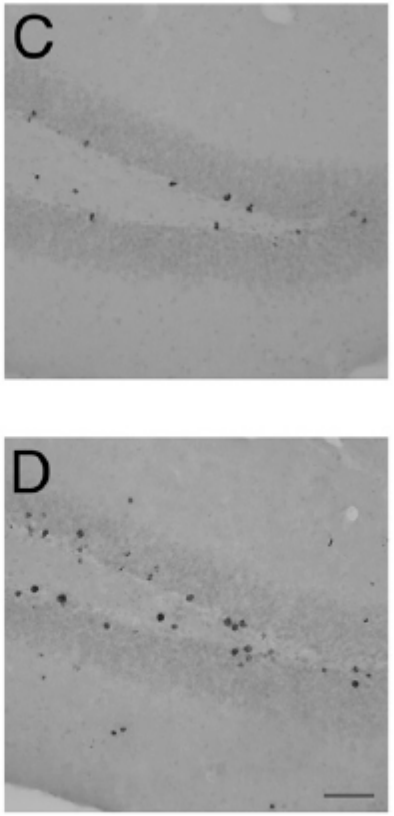
Henriette
Van Praag

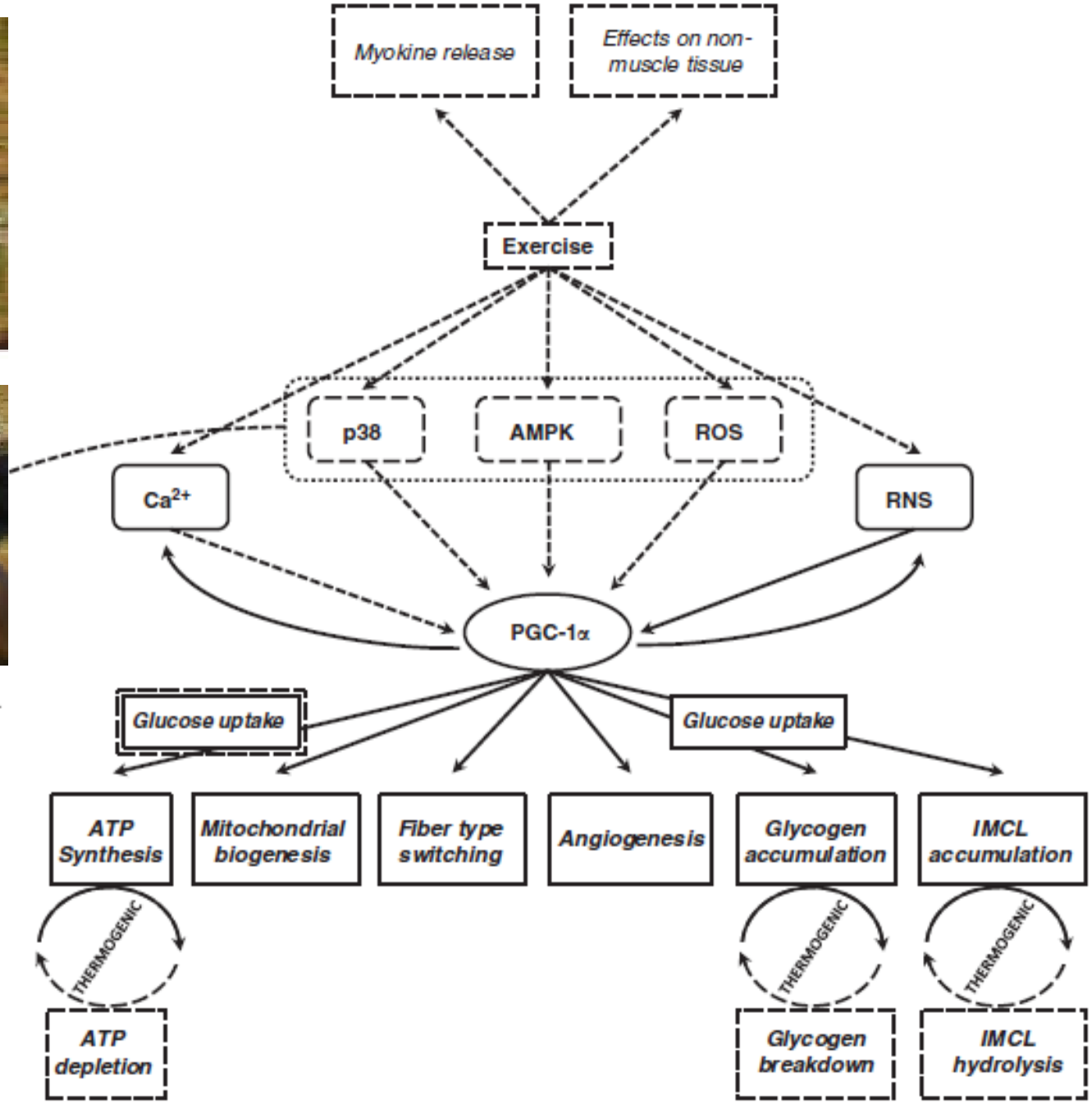
Running enhances spatial pattern separation in mice

Creer DJ, Romberg C, Saksida LM, van Praag H, Bussey TJ. *Proc Natl Acad Sci U S A.* 2010; 107:2367-72.



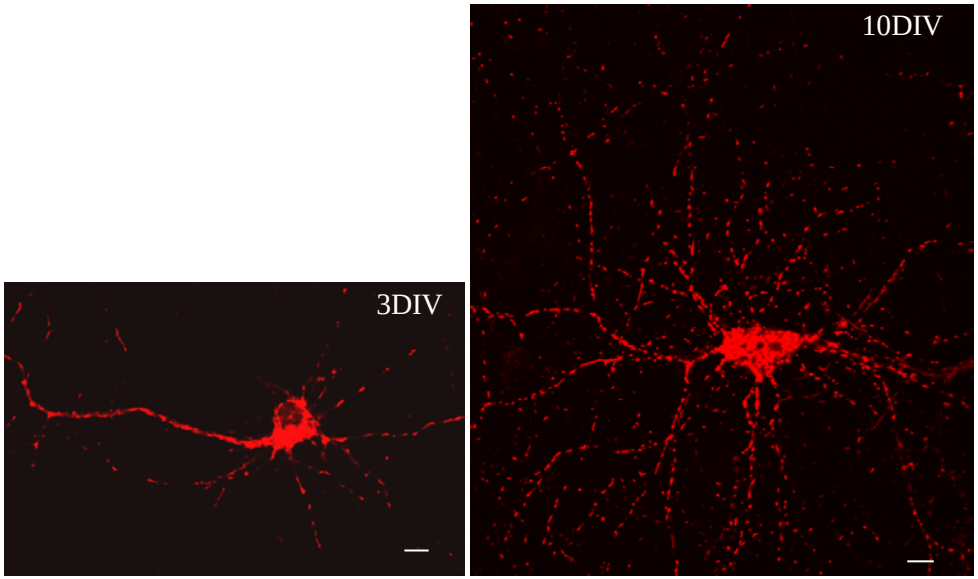


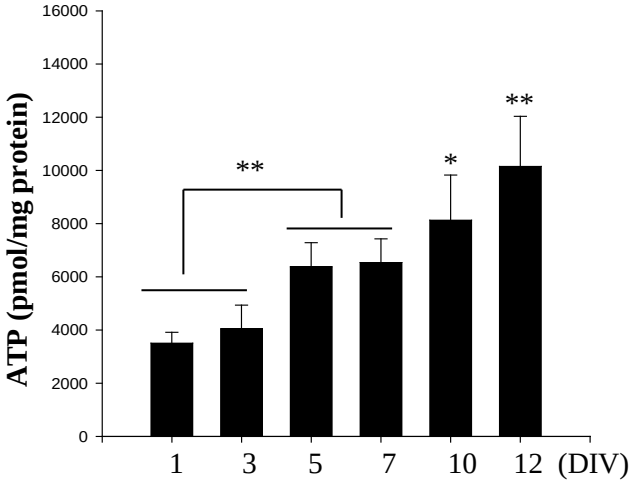


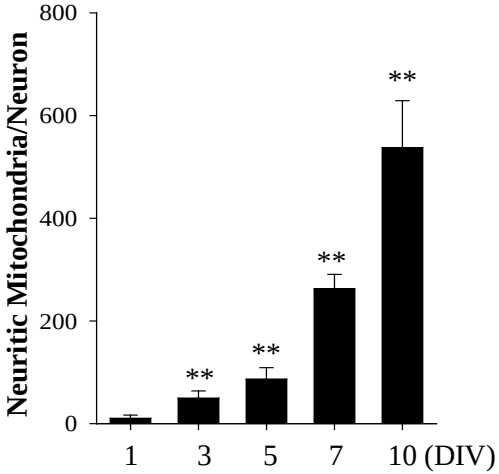


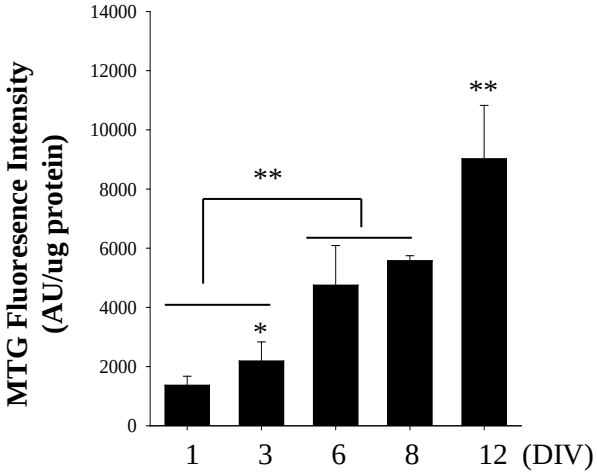
Summermatter and Handschin, 2012

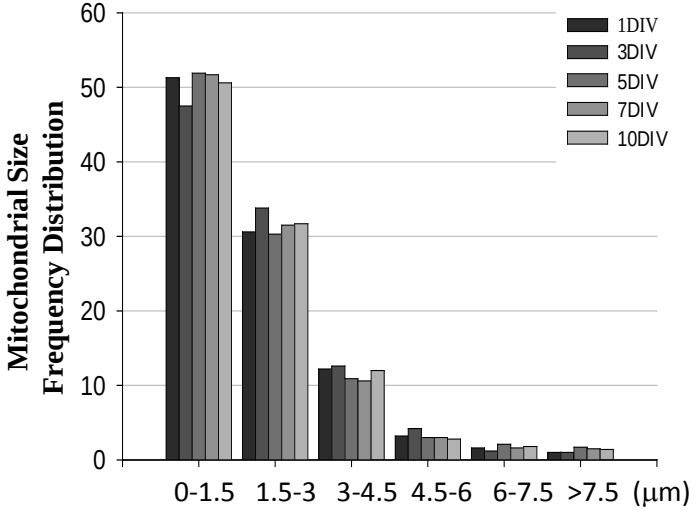
The number of mitochondria and ATP levels increase in hippocampal neurons as they grow and form synapses





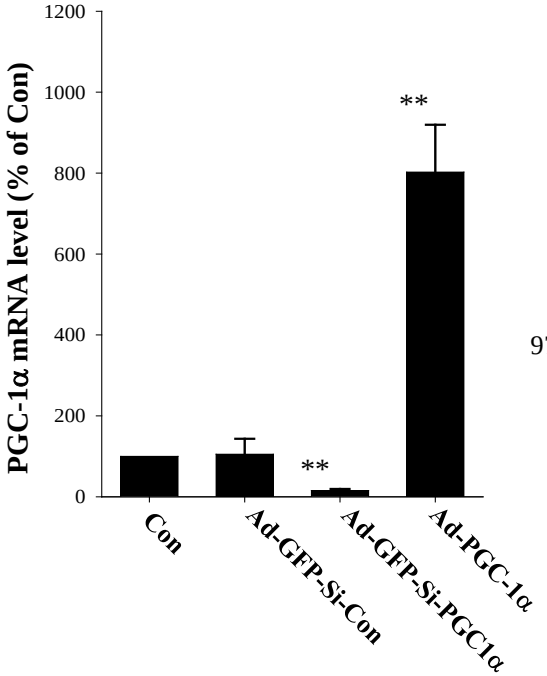


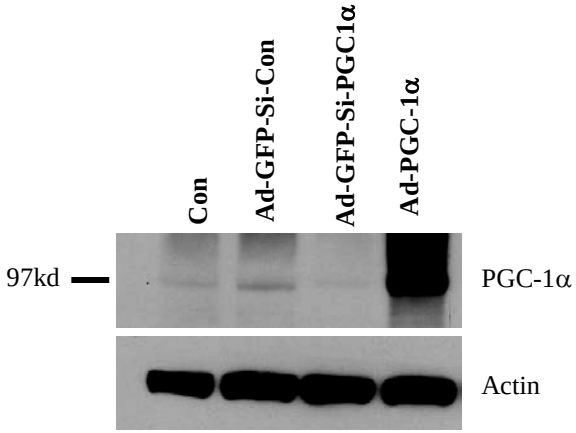


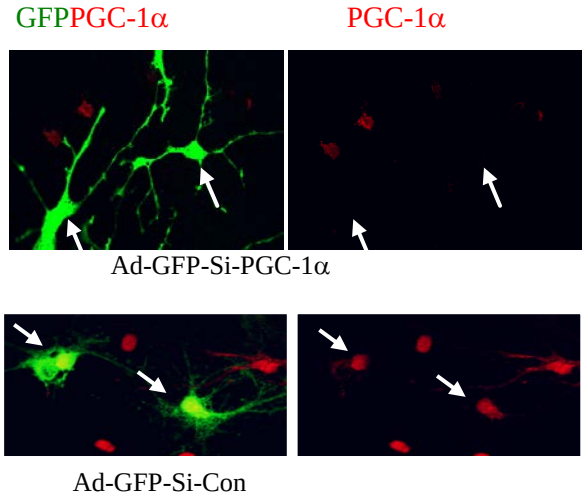


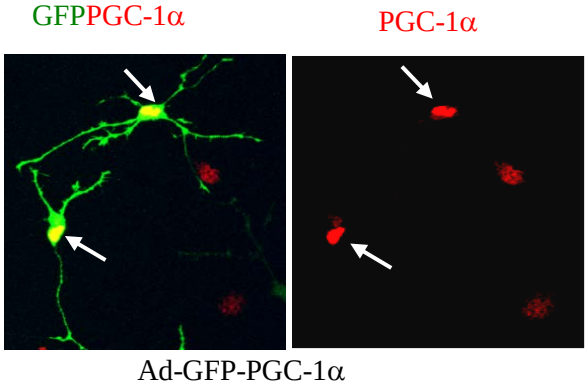
Cheng A et al. (2012) Involvement of PGC-1α in the formation and maintenance of neuronal dendritic spines. *Nature Commun.* Dec 4; 3:1250.

PCGC-1α levels can be selectively reduced or increased in hippocampal neurons using genetically engineered adenoviruses

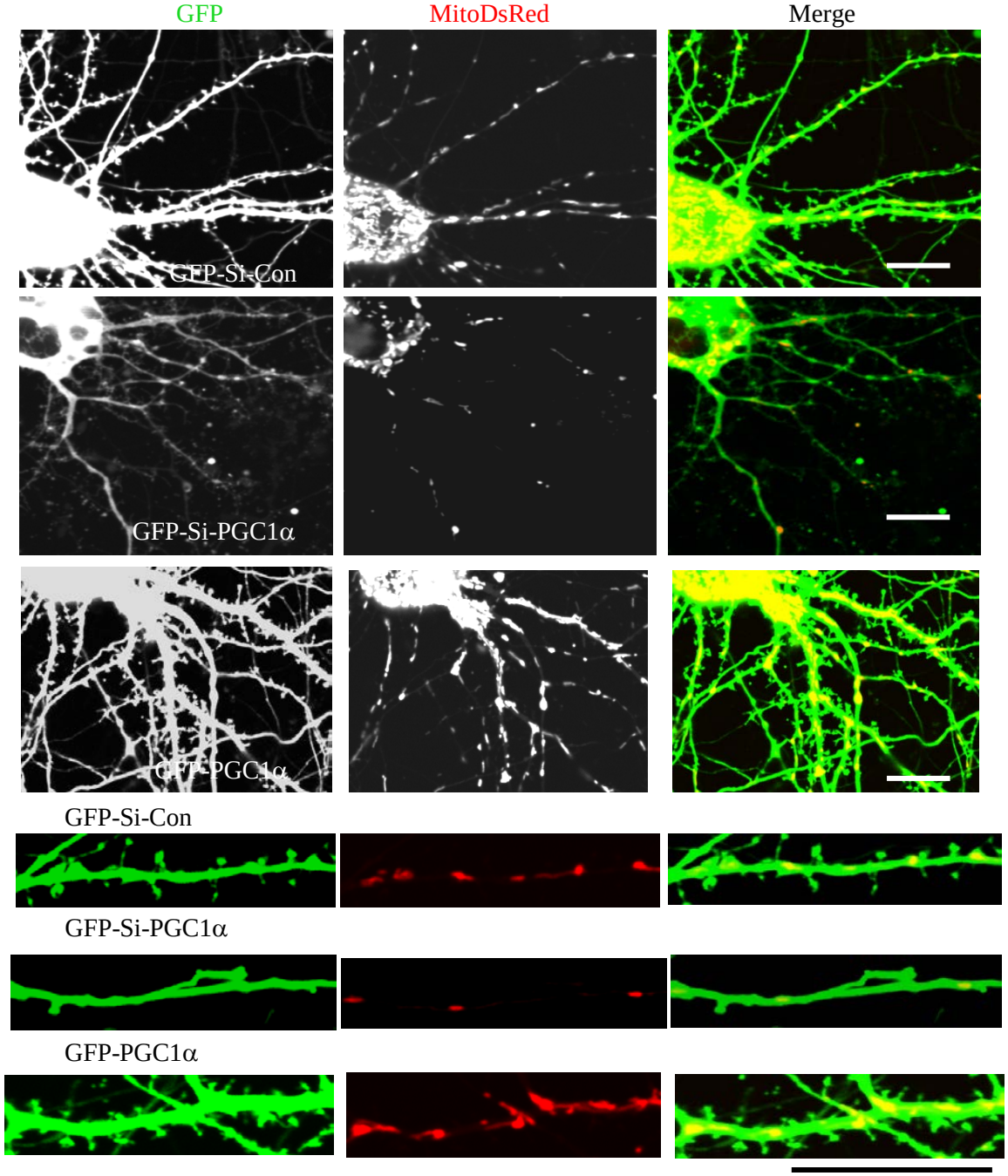




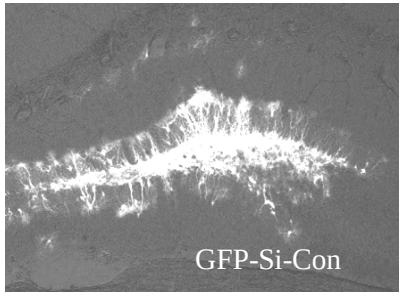


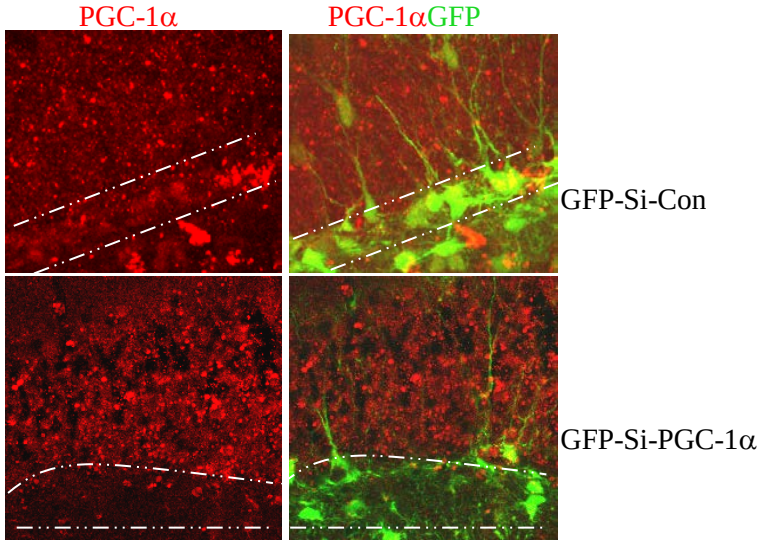


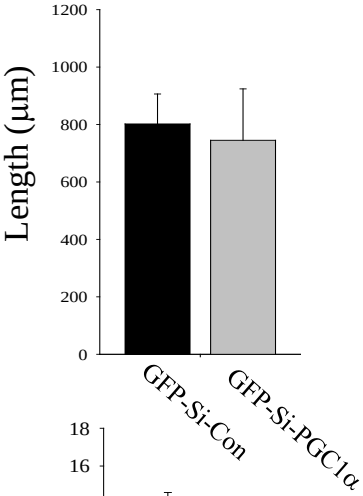
PCGC-1α plays a critical role in synapse formation in developing hippocampal neurons

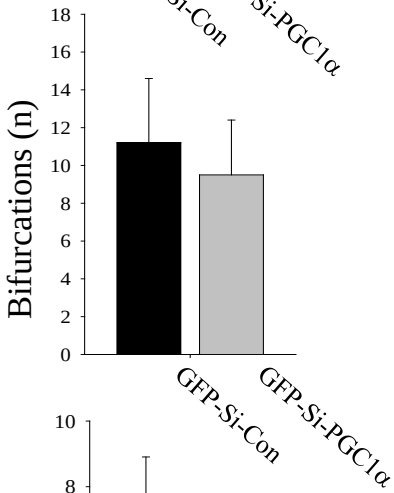


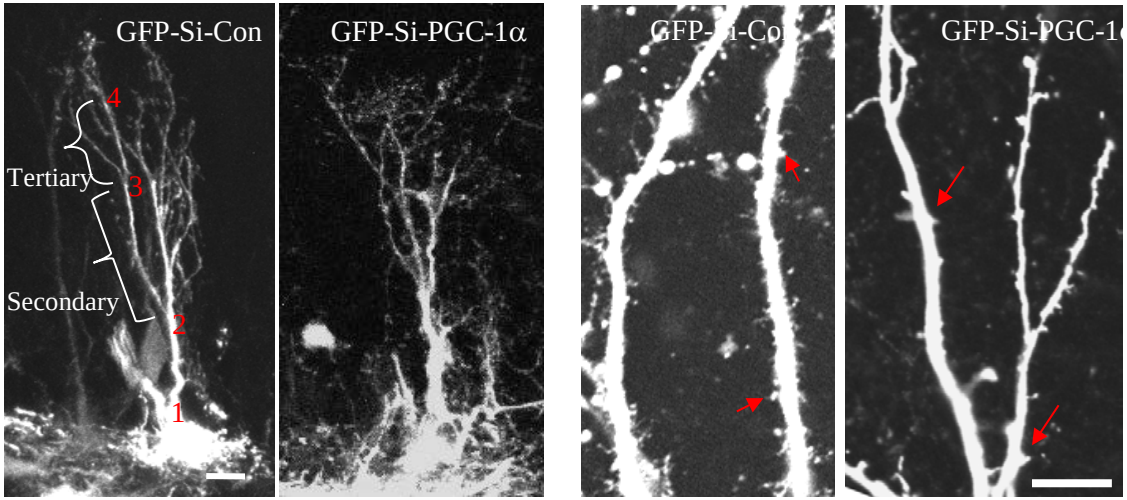
PCGC-1α plays a critical role in the maintenance of synapses in the adult hippocampus

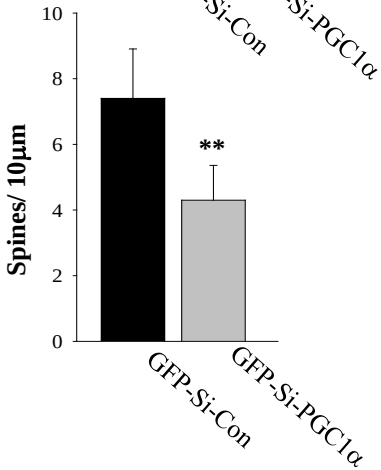




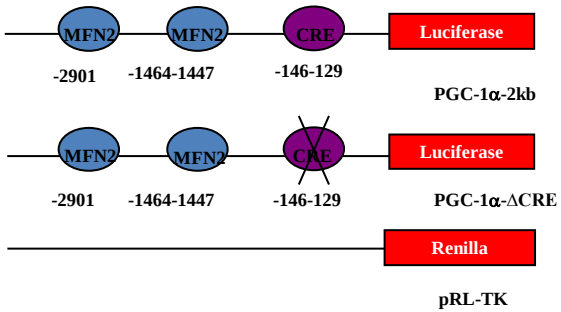


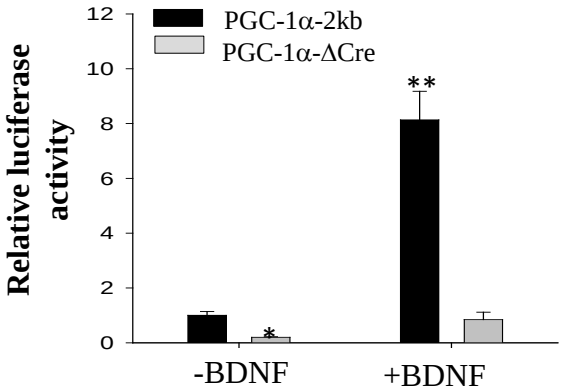


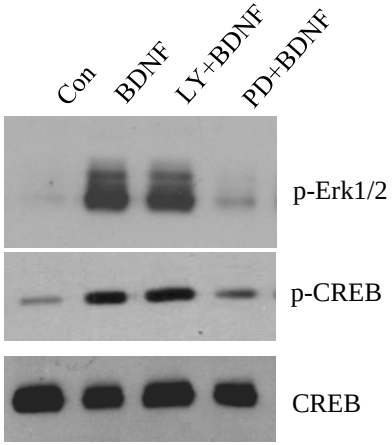


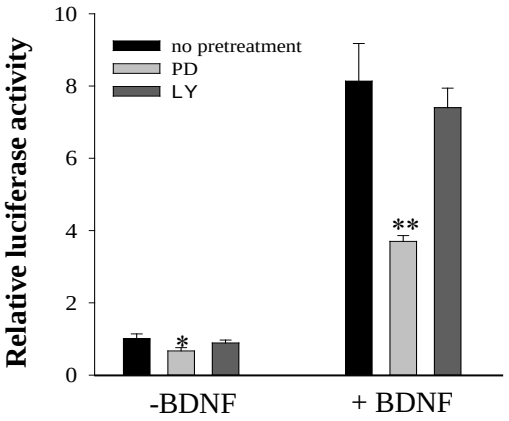


Brain-derived neurotrophic factor (BDNF) stimulates PGC-1α promoter activity by a CREB-mediated mechanism

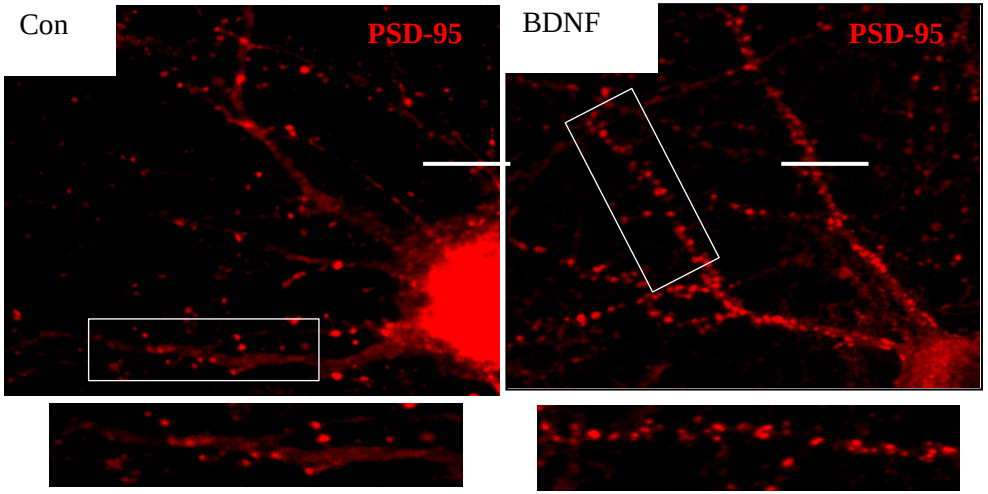


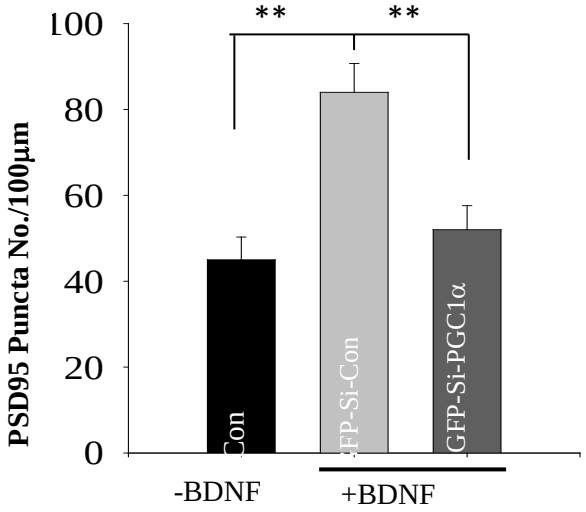


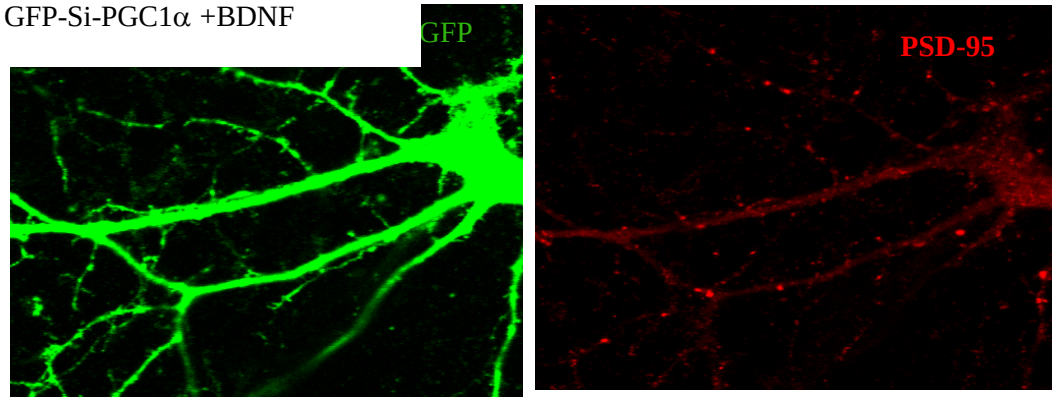


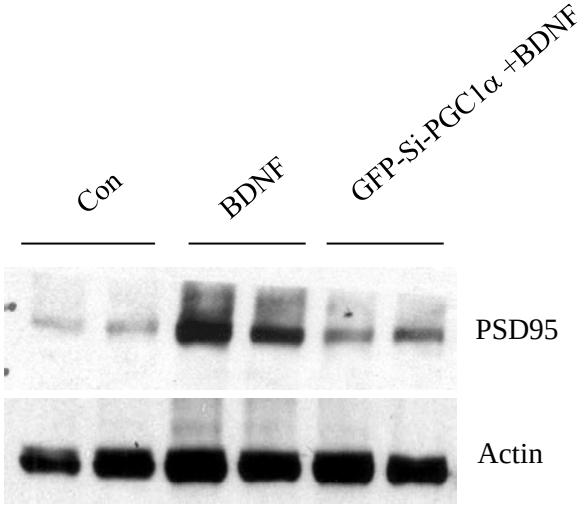


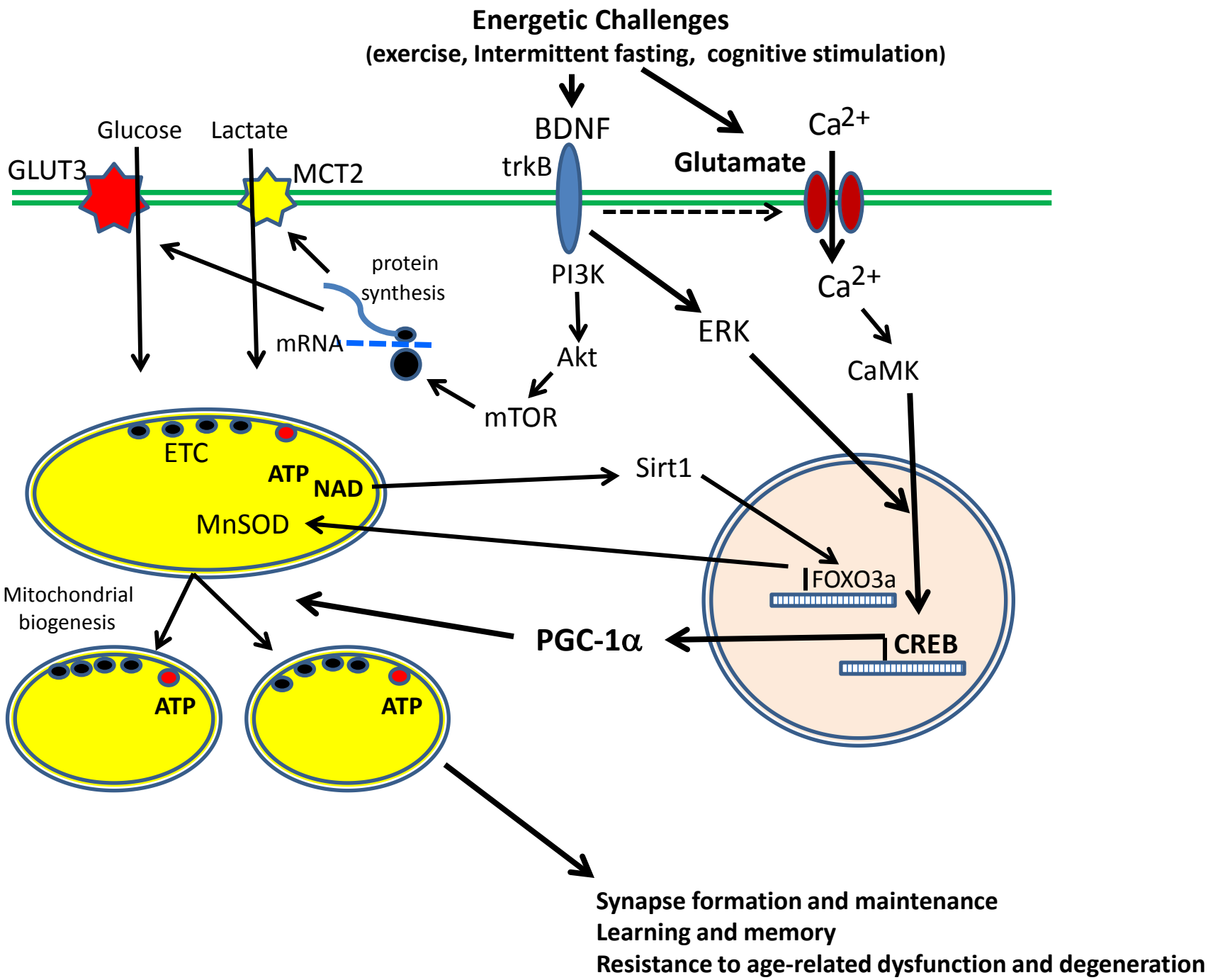
Enhancement of synapse formation by BDNF requires PCGC-1α



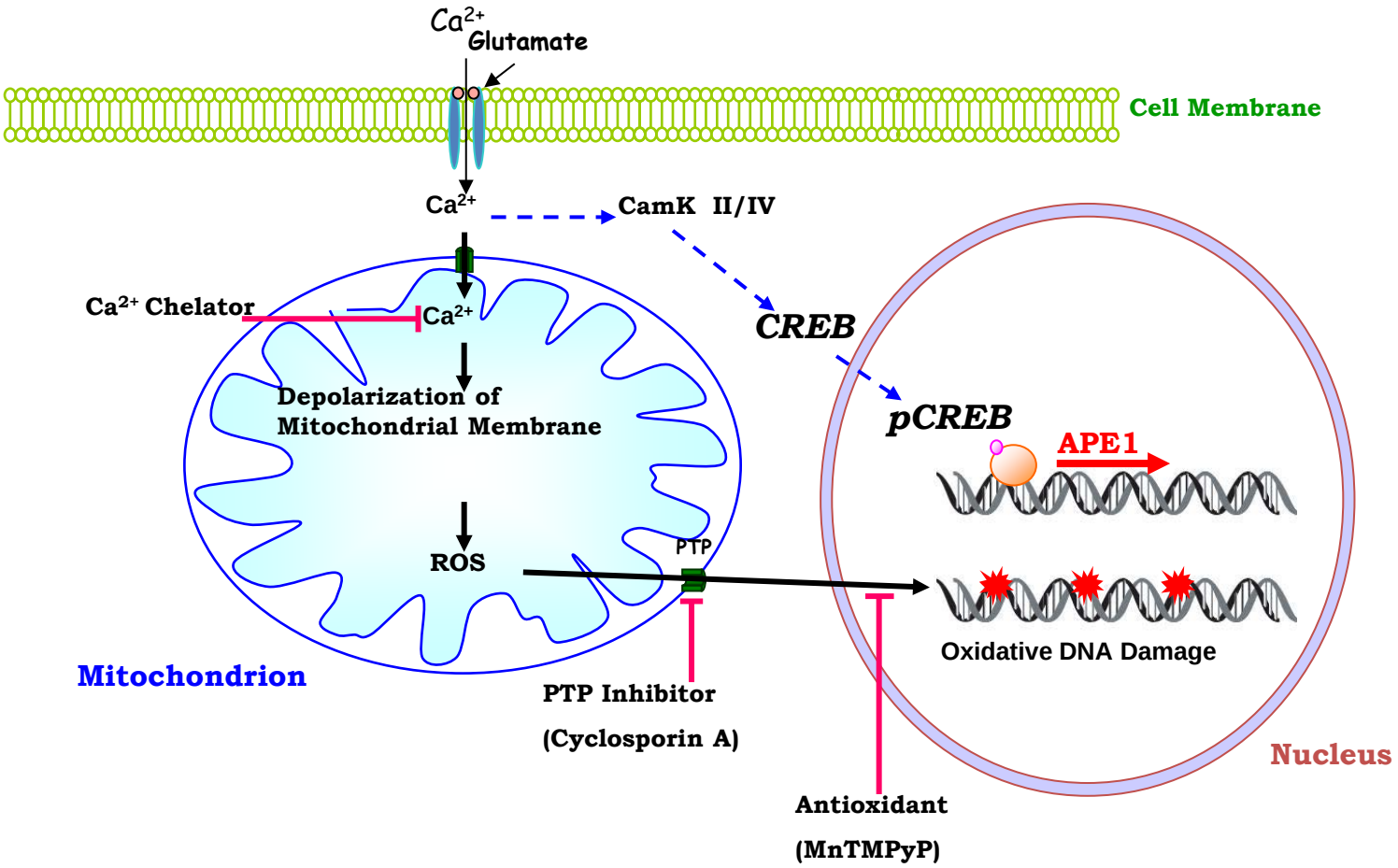






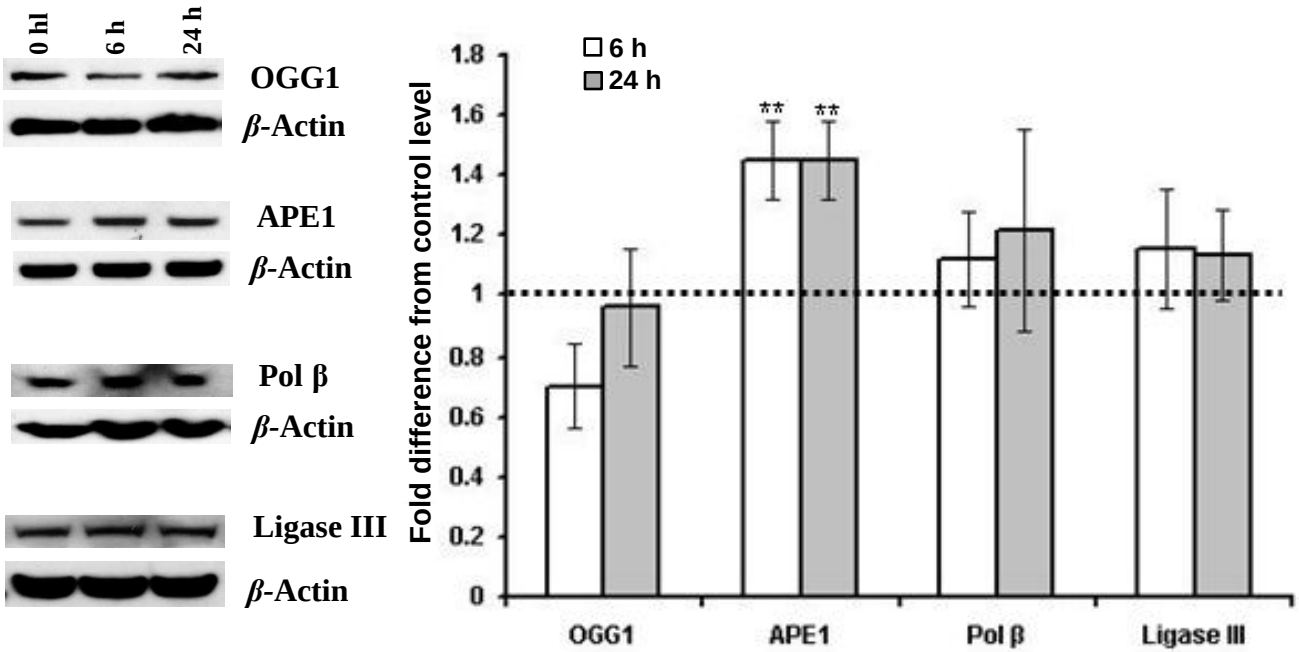

Energetic Challenges
(exercise, Intermittent fasting, cognitive stimulation)
BDNF
Glutamate
Ca2+
Glucose
Lactate
GLUT3
MCT2
trkB
protein synthesis
mRNA
PI3K
Akt
mTOR
ERK
Ca2+
CaMK
ETC
ATP
NAD
MnSOD
Sirt1
FOXO3a
CREB
PGC-1α
Mitochondrial biogenesis
ATP
ATP
Synapse formation and maintenance
Learning and 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.



Yang JL, Tadokoro T, Keijzers G, Mattson MP, Bohr VA. Neurons efficiently repair glutamate-induced DNA damage by a process involving CREB-mediated up-regulation of apurinic endonuclease 1. *J Biol Chem.* 2010; 285:28191-9.

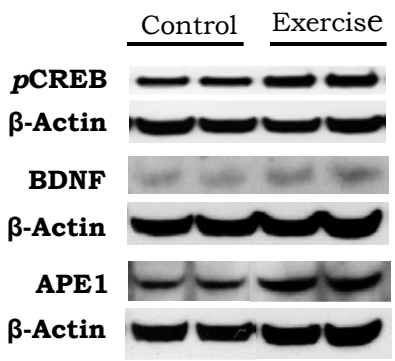
BDNF increases levels of APE1 in cultured cerebral cortical neurons

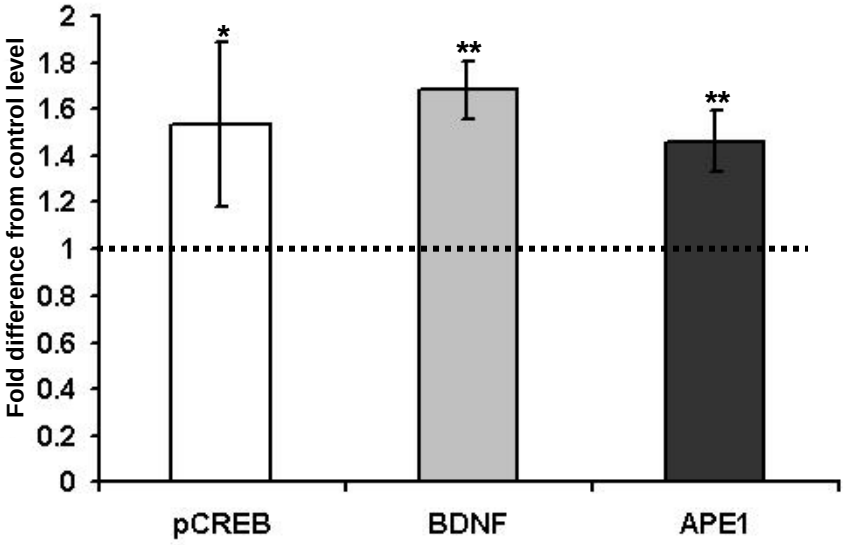


Yang JL, Lin YT, Chuang PC, Bohr VA, Mattson MP. BDNF and Exercise Enhance Neuronal DNA Repair by Stimulating CREB-Mediated Production of Apurinic/Apyrimidinic Endonuclease 1. Neuromolecular Med. 2013 Oct 10. [Epub ahead of print].

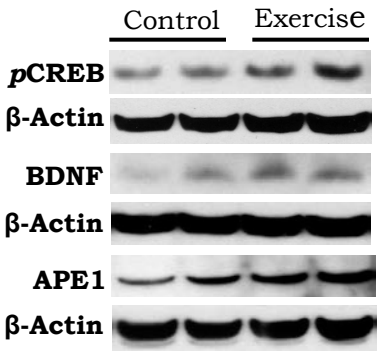
Exercise increases BDNF levels, CREB activation and APE1 levels in mouse brain cells in vivo

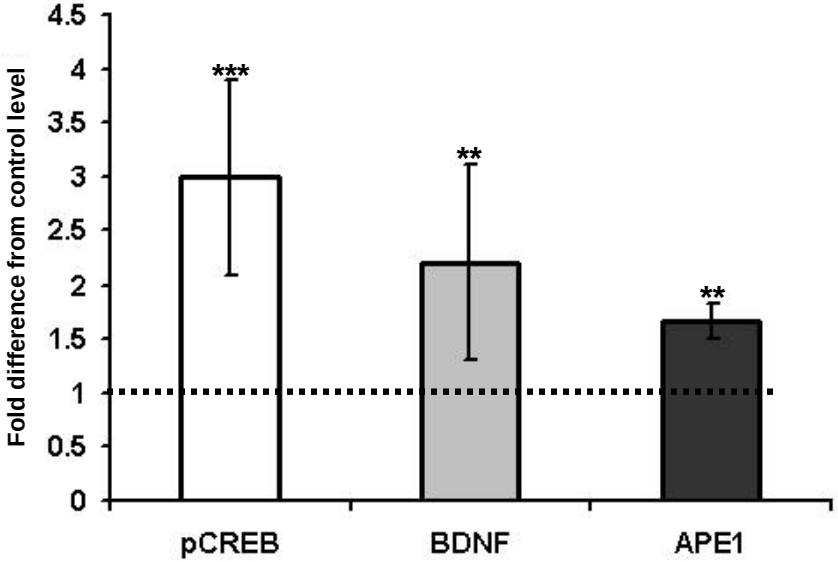
Cerebral Cortex



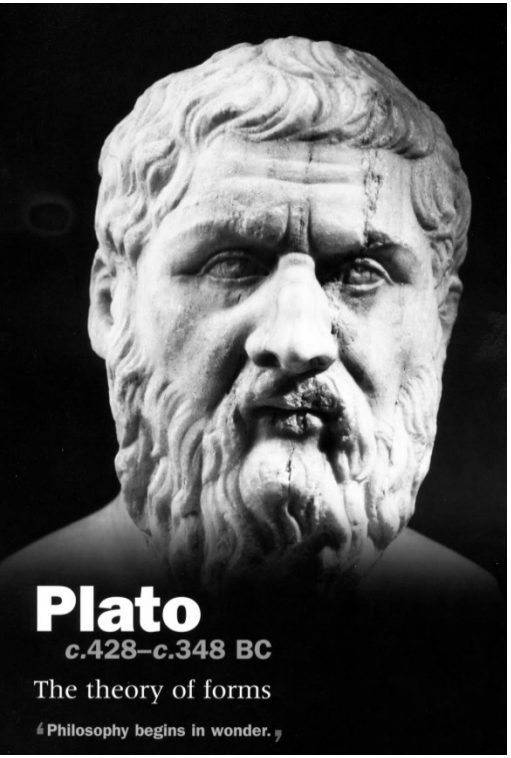


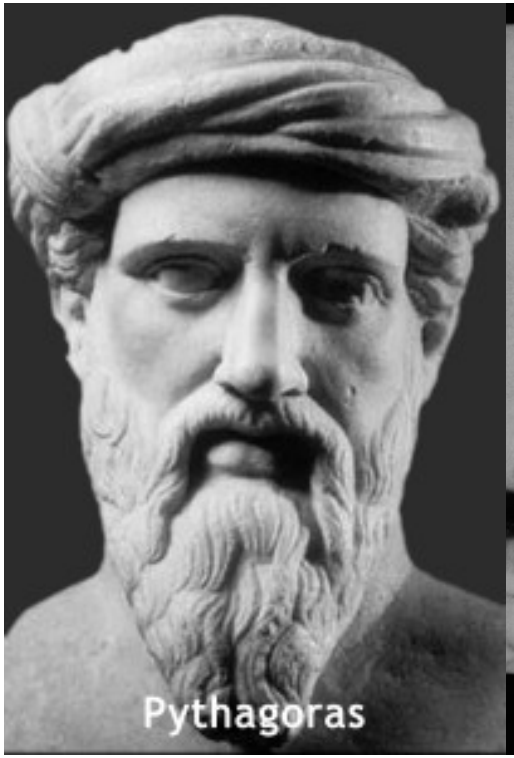
Hippocampus

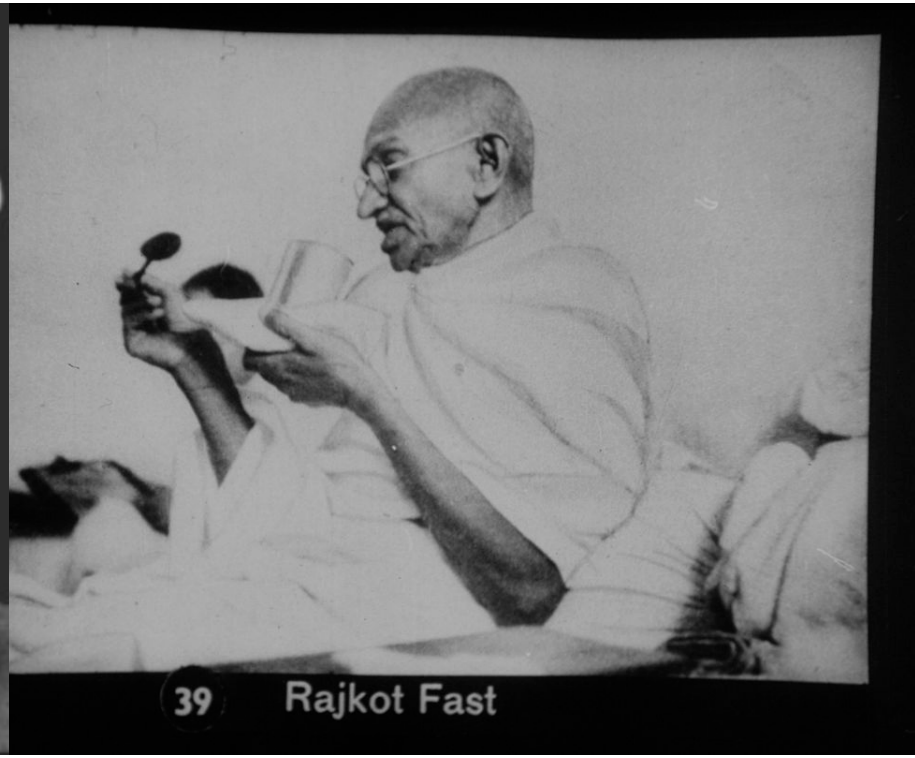




Historical Perspective "I fast for greater physical and mental efficiency." Plato







"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.

The Fasting Cure
by
UPTON SINCLAIR

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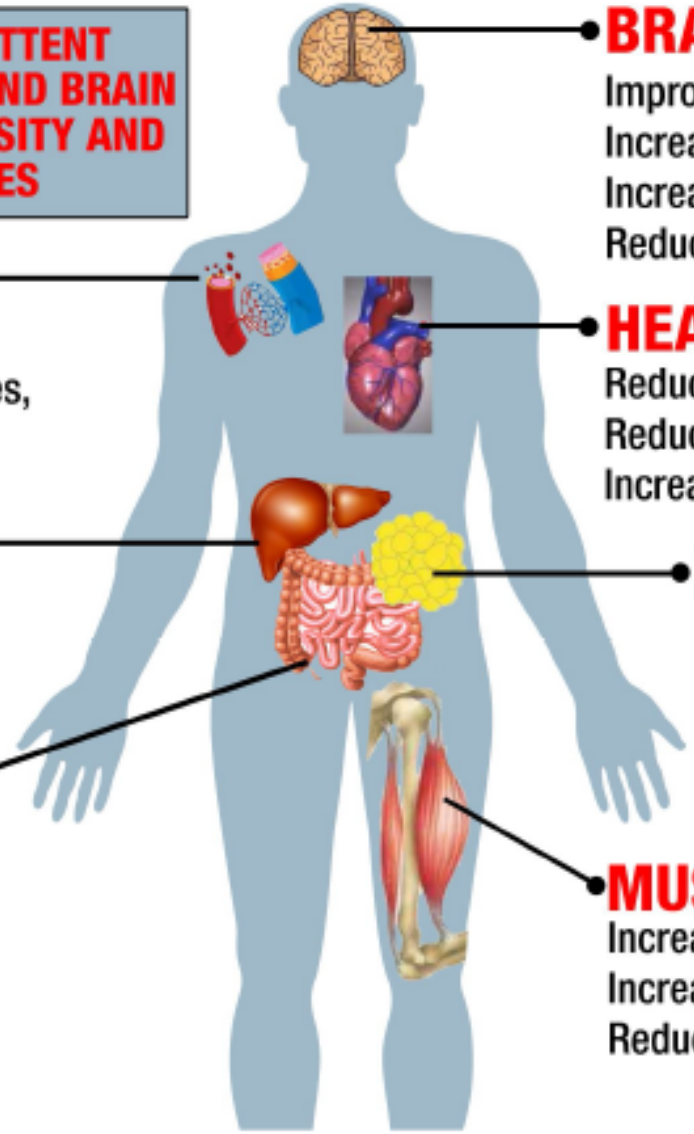
MITCHELL KENNERLEY

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

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

HEART
Reduced resting heart rate
Reduced blood pressure
Increased stress resistance

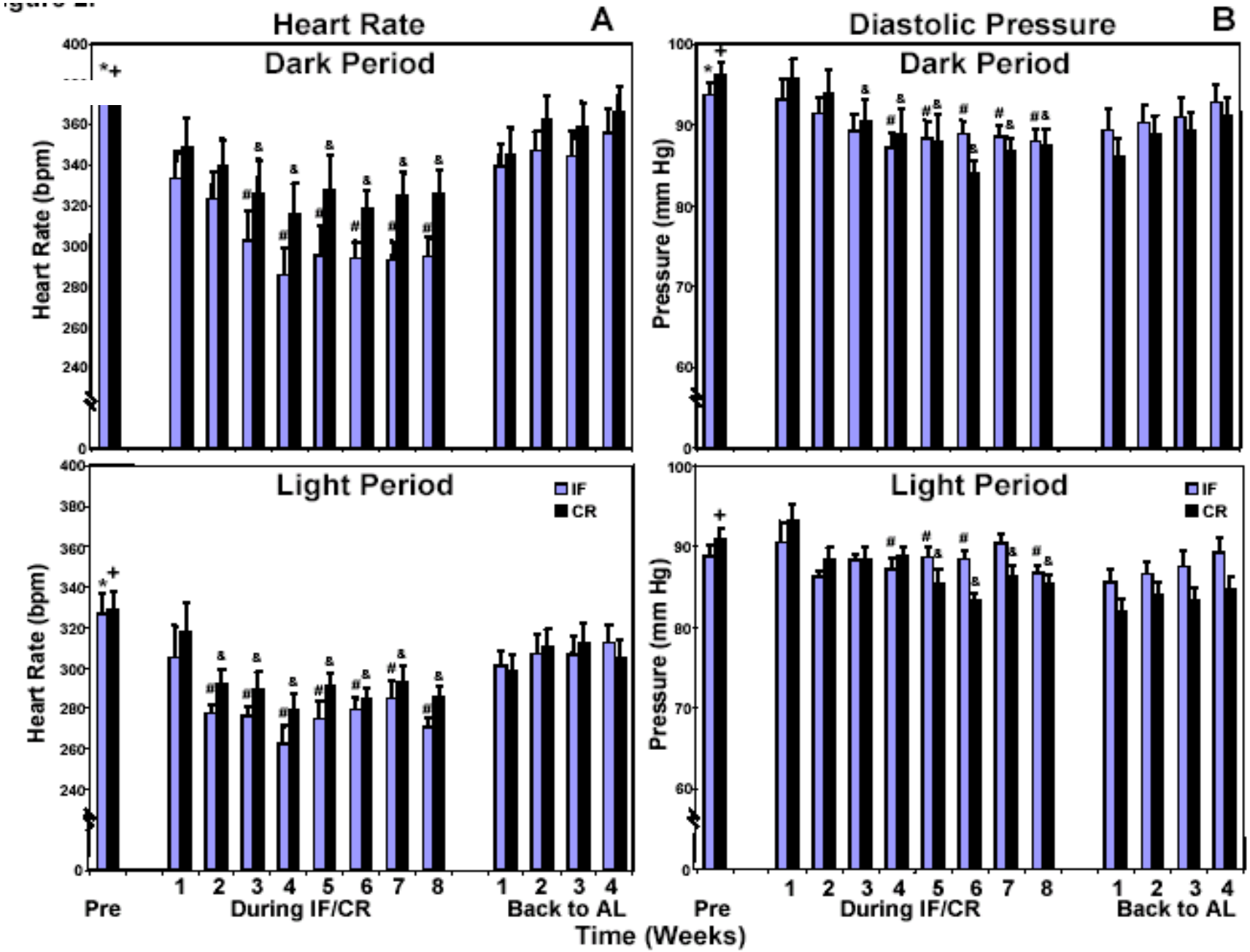
LIVER
Increased insulin sensitivity
Ketone body production
Decreased IGF-1 levels

FAT CELLS
Lipolysis
Reduced leptin
Increased adiponectin
Reduced inflammation

INTESTINES
Reduced energy uptake
Reduced inflammation
Reduces cell proliferation

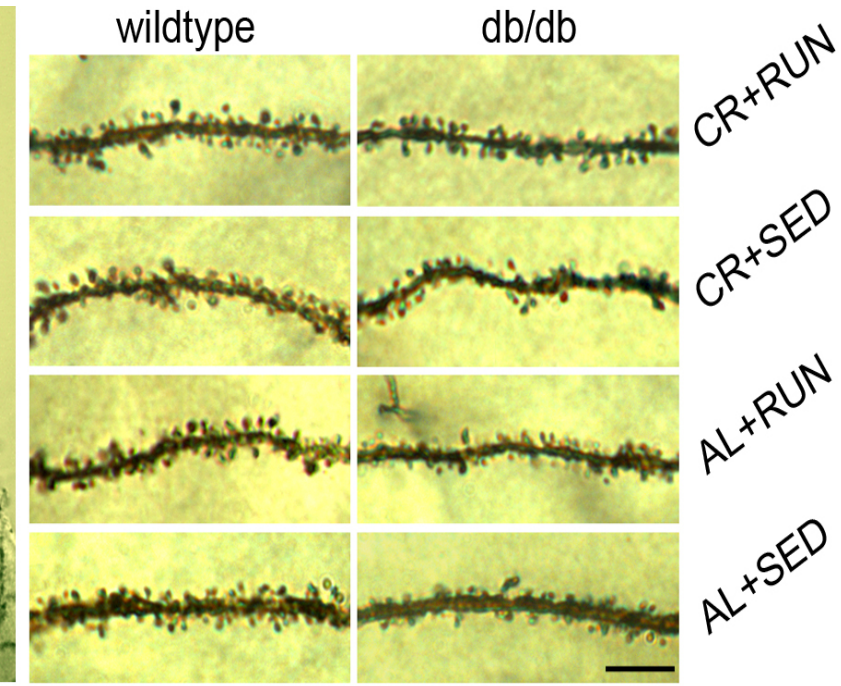
MUSCLE
Increased insulin sensitivity
Increased efficiency
Reduced inflammation

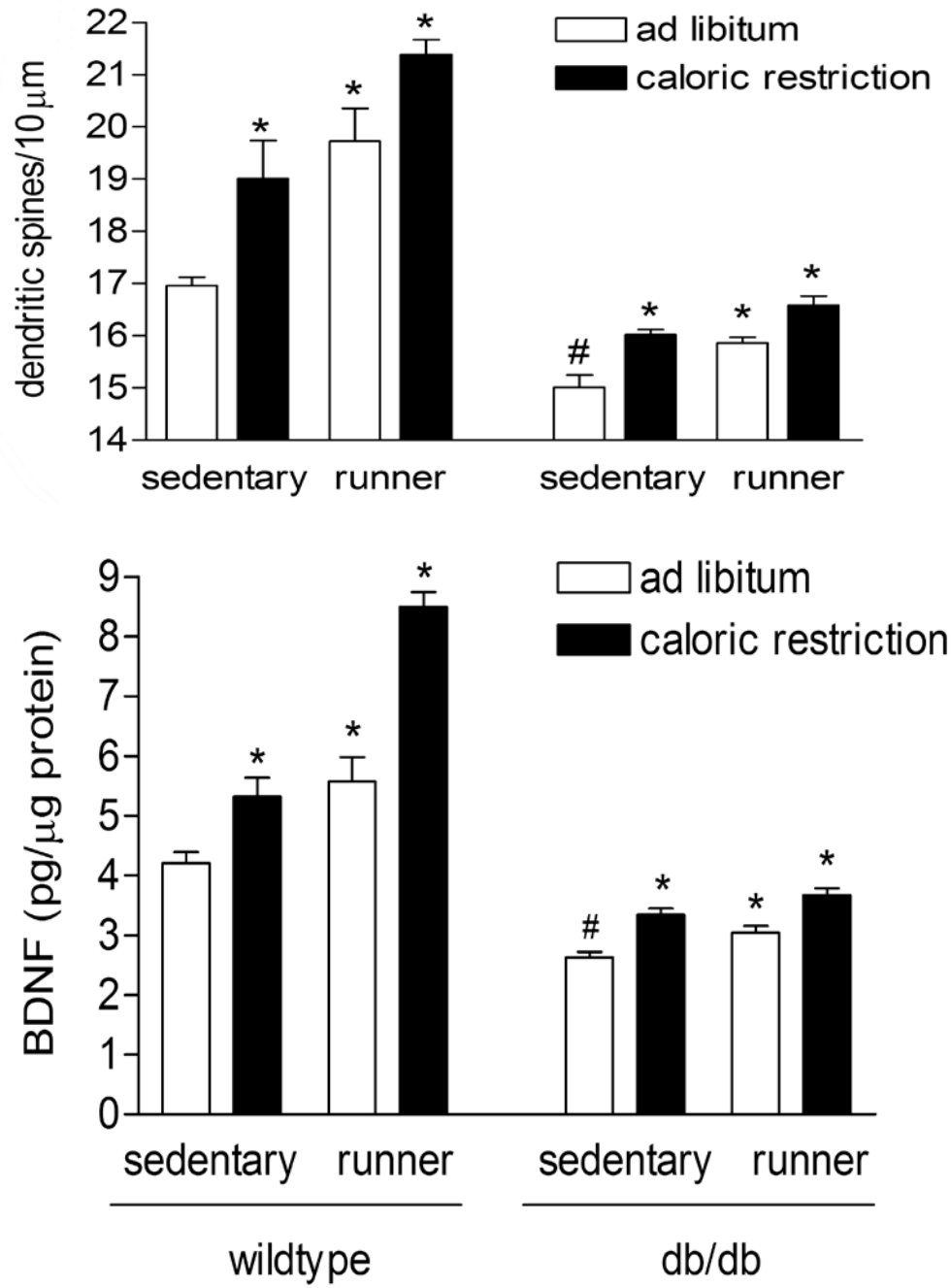
IF Promotes Fat 'Burning' and the Production of Beneficial Ketones



Mager DE, Wan R, Brown M, Cheng A, Wareski P, Abernethy DR, Mattson MP. (2006) Caloric restriction and intermittent fasting alter spectral measures of heart rate and blood pressure variability in rats. FASEB J. 20:631-7.

Evolutionary Perspective: Our hunter/gatherer ancestors would not have survived unless their brain was functioning at high level when they were hungry.





Stranahan et al. (2008) *Nature Neurosci.* 11:309-317 .
Stranahan et al. (2009) *Hippocampus* 19: 951-961.

Annals of Neurology Vol 45 No 1 January 1999

Food Restriction Reduces Brain Damage and Improves Behavioral Outcome Following Excitotoxic and Metabolic Insults

Annadora J. Bruce-Keller, PhD,*† Gloria Umberger, BS, MPH,† Robert McFall, BS,* and Mark P. Mattson, PhD*†

PNAS | March 4, 2003 | vol. 100 | no. 5 | 2911–2916

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 Ruiqian Wan, PhD[1]

Neurobiology of Aging 34 (2013) 928–935

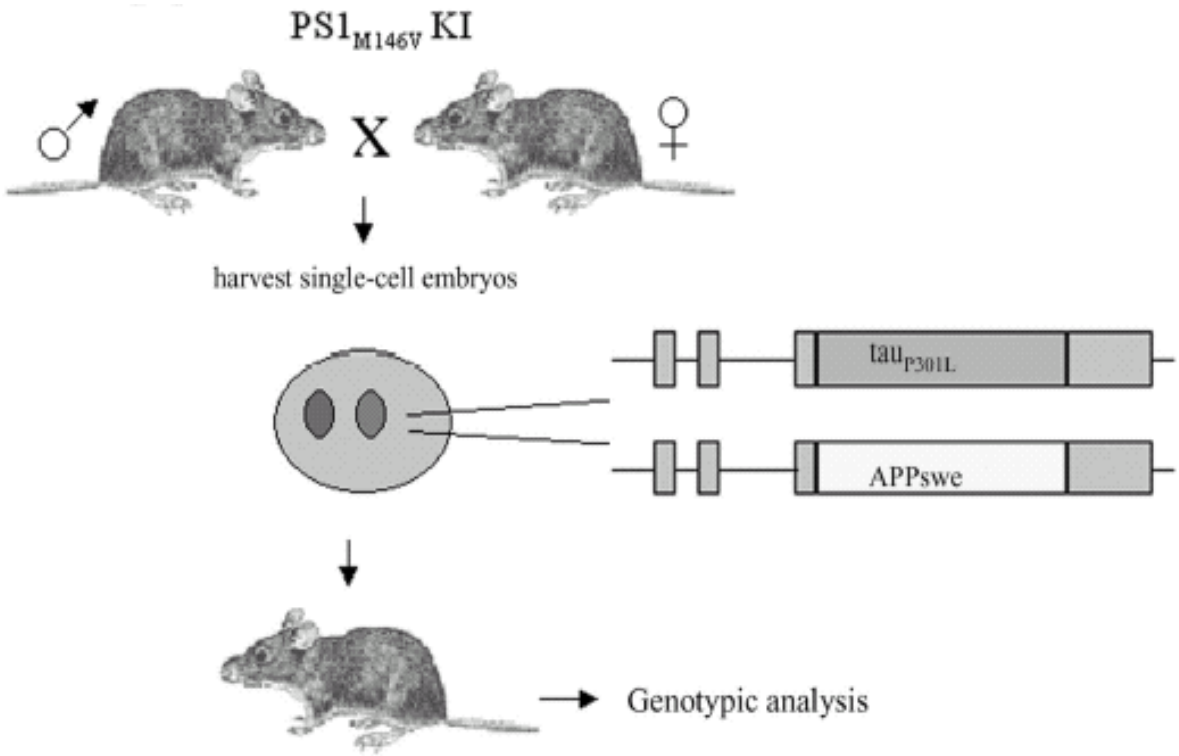
Dietary energy intake modifies brainstem autonomic dysfunction caused by mutant α-synuclein

Kathleen J. Griffioen[a], Sarah M. Rothman[a], Bruce Ladenheim[b], Ruiqian Wan[a], Neil Vranis[a], Emmette Hutchison[a], Eitan Okun[a,c], Jean Lud Cadet[b], Mark P. Mattson[a,d,*]

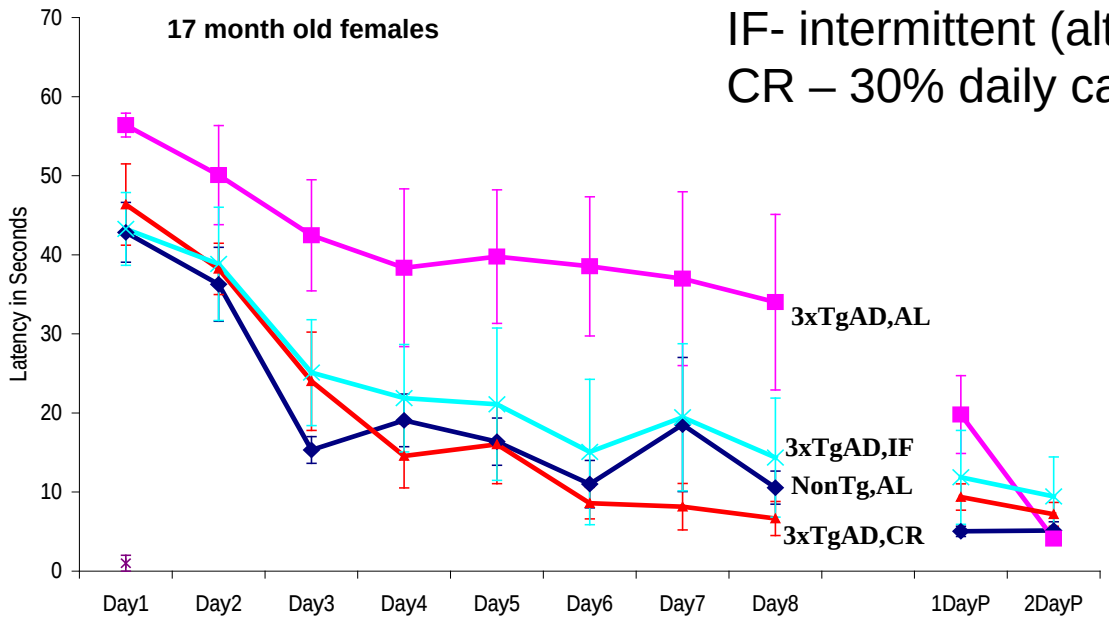
Neuron, Vol. 39, 1–20, July 31, 2003, Copyright ©2003 by Cell Press

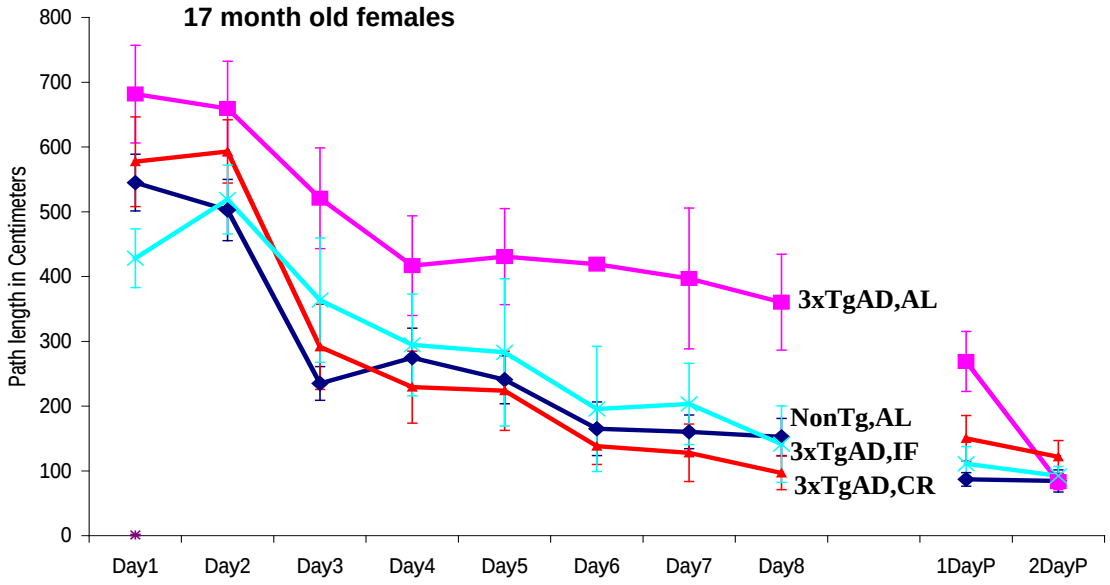
Triple-Transgenic Model of Alzheimer's Disease with Plaques and Tangles: Intracellular Aβ and Synaptic Dysfunction

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. LaFerla[1,*]



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





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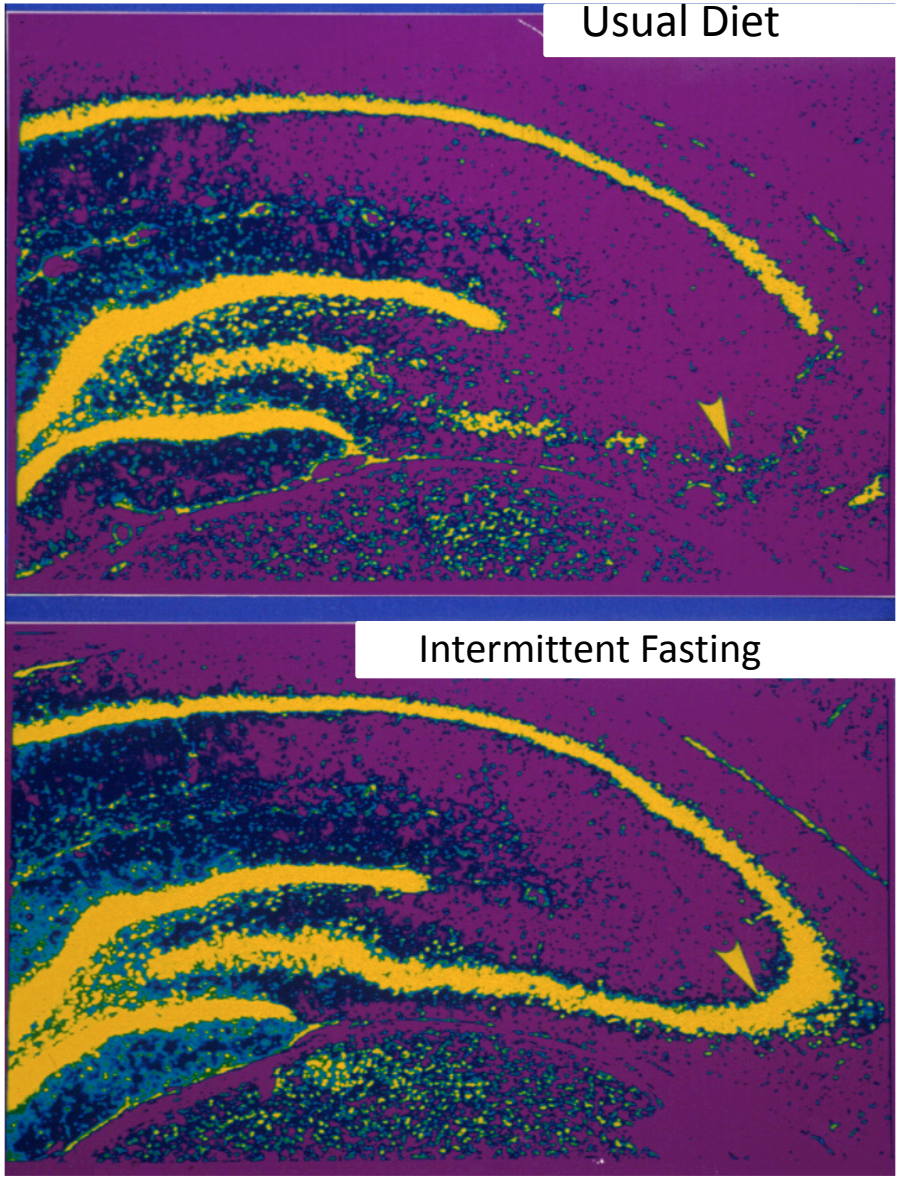
Neurobiol Dis. 26:212-20.

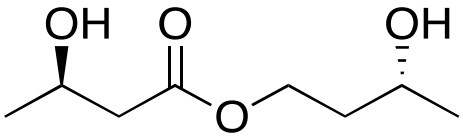
DISPELLING THE DEMONS (epileptic seizures)

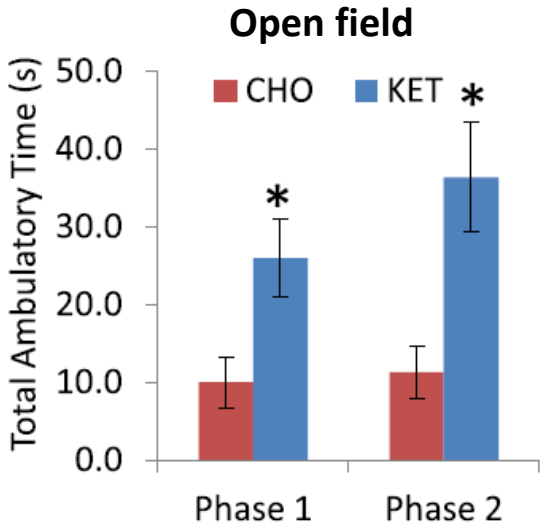
Romans: Fasting

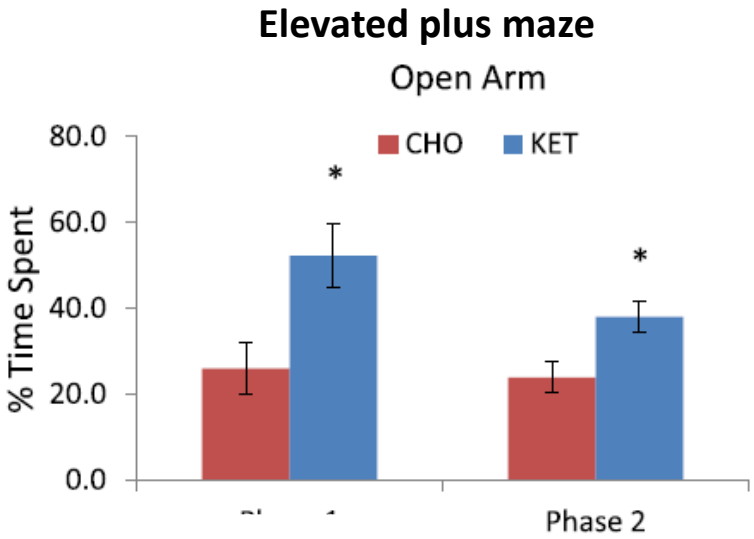
Bruce-Keller, A. J., G. Umberger, R. McFall and M. P. Mattson (1999) **Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults.** *Ann. Neurol.* 45: 8-15.

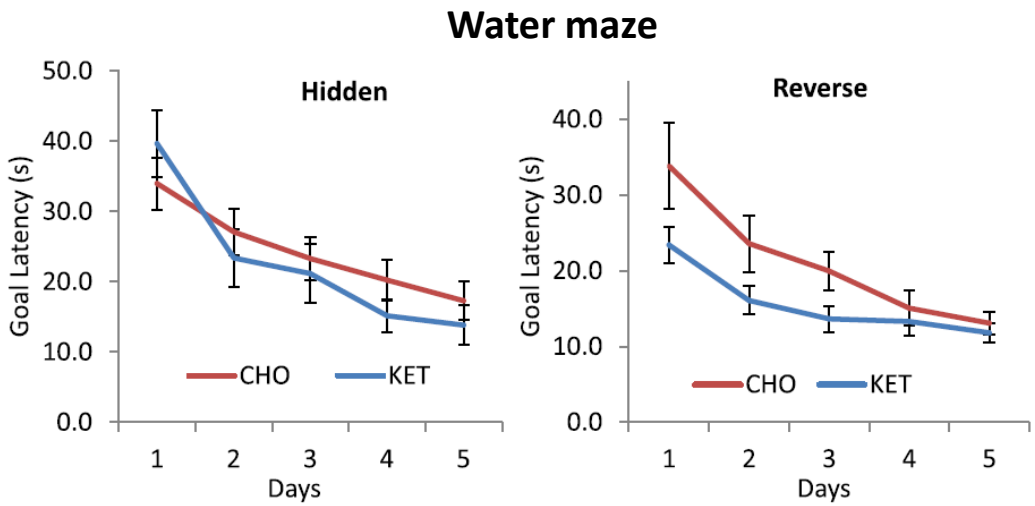


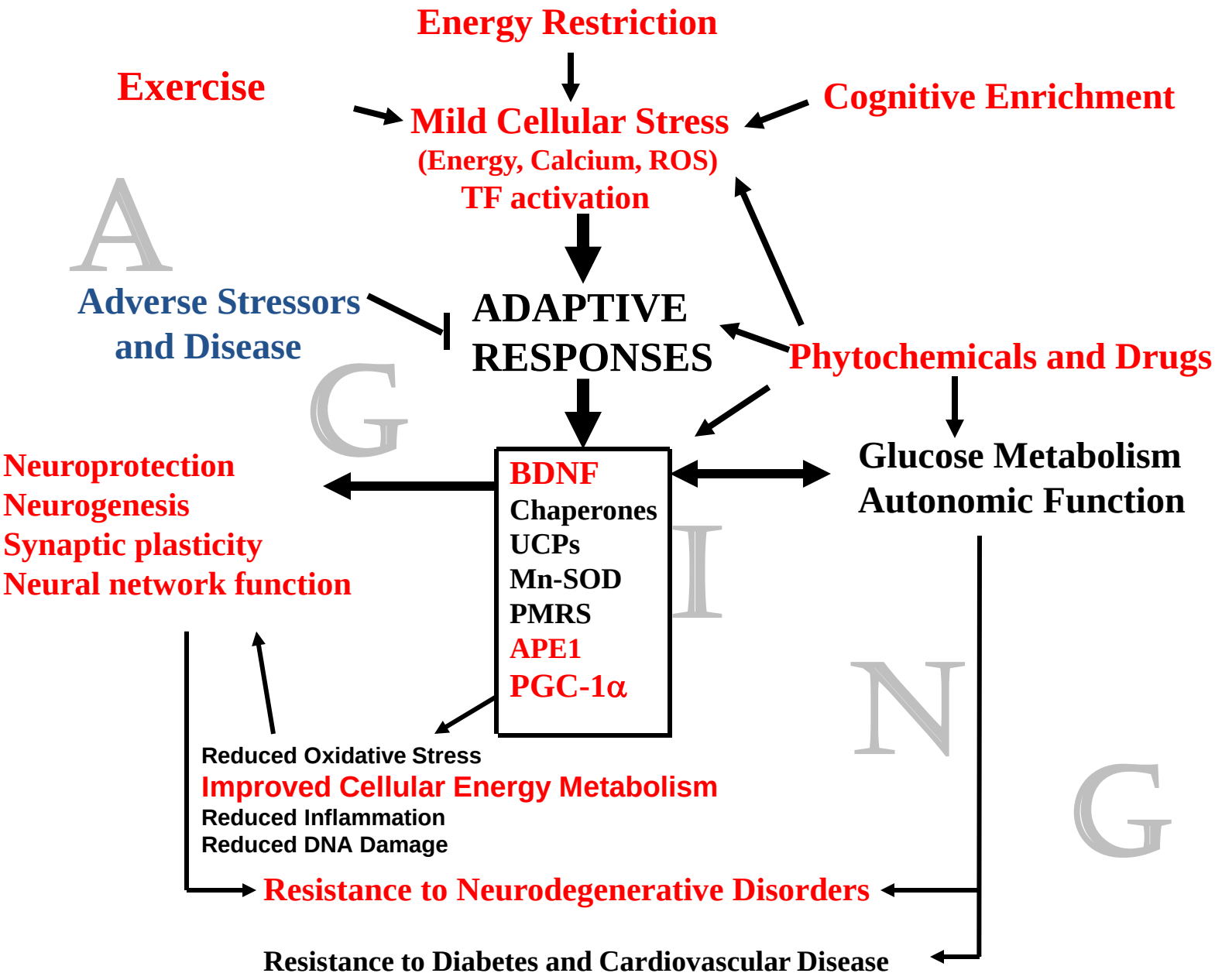
Kashiwaya, Y., C. Bergman, J. H. Lee, R. Wan, M. T. King, M. R. Mughal, E. Okun, K. Clarke, M. P. Mattson and R. L. Veech (2013) **A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease.** *Neurobiol. Aging* 34(6): 1530-9..










Energy Restriction
Exercise
Cognitive Enrichment
Mild Cellular Stress
(Energy, Calcium, ROS)
TF activation
A
Adverse Stressors
and Disease
ADAPTIVE
RESPONSES
Phytochemicals and Drugs
G
Neuroprotection
Neurogenesis
Synaptic plasticity
Neural network function
BDNF
Chaperones
UCPs
Mn-SOD
PMRS
APE1
PGC-1α
Glucose Metabolism
Autonomic Function
I
N
G
Reduced Oxidative Stress
Improved Cellular Energy Metabolism
Reduced Inflammation
Reduced DNA Damage
Resistance to Neurodegenerative Disorders
Resistance to Diabetes and Cardiovascular Disease