"The Brain, Energy Metabolism and Hormetic Pathways to Optimal Health"

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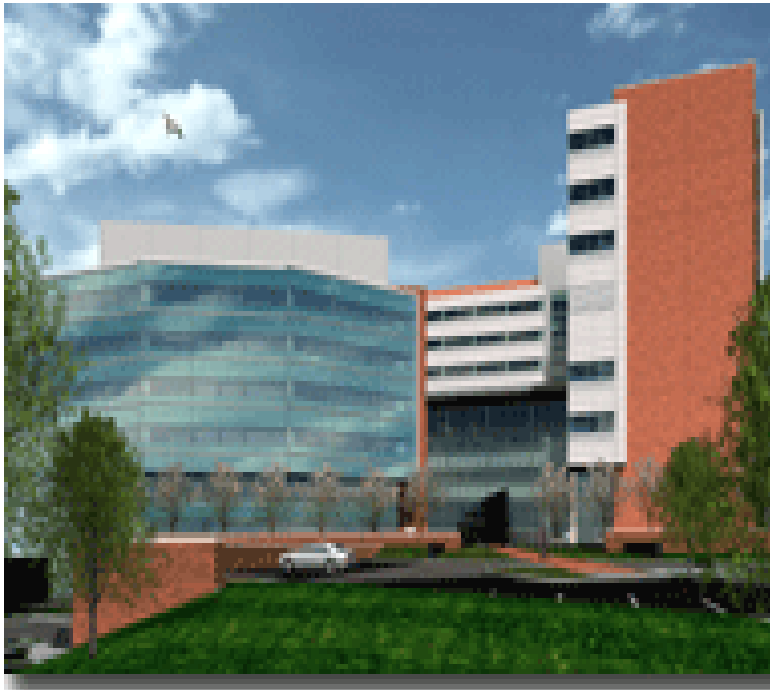
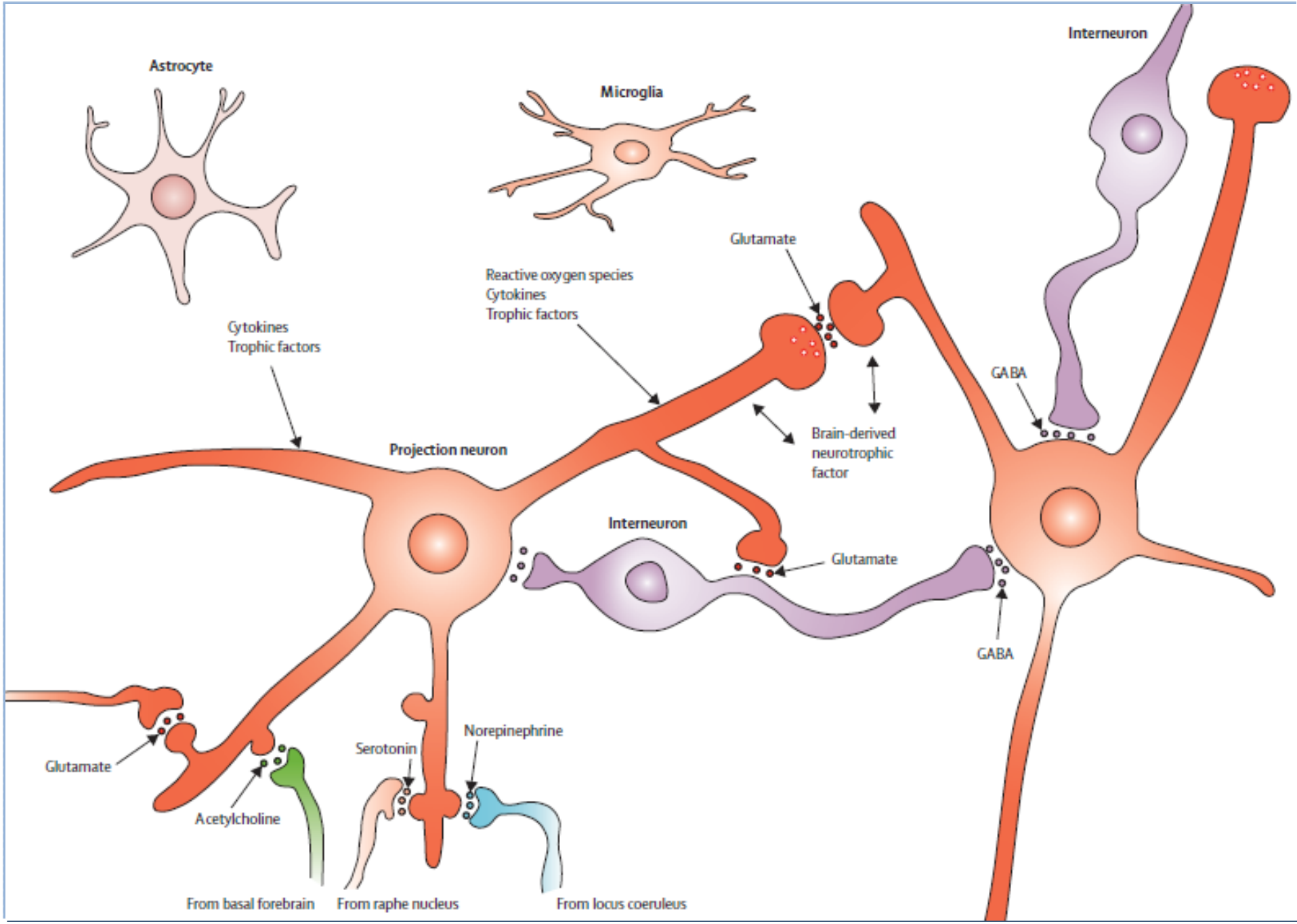
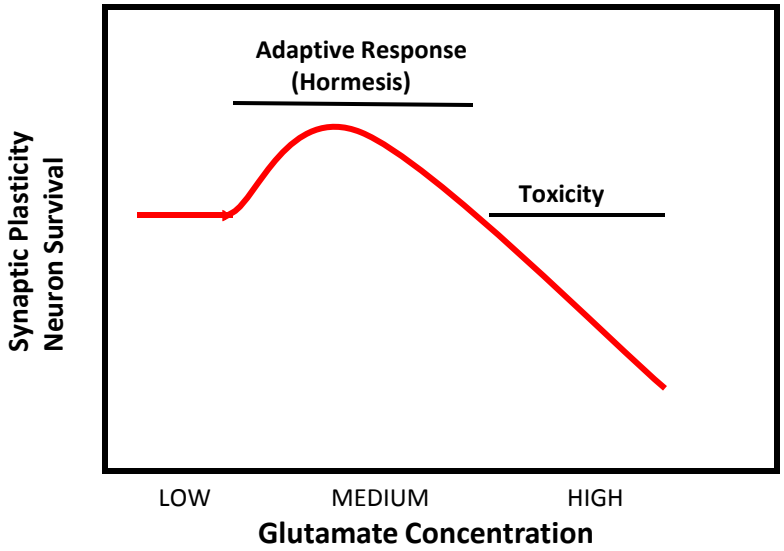
Baltiimore

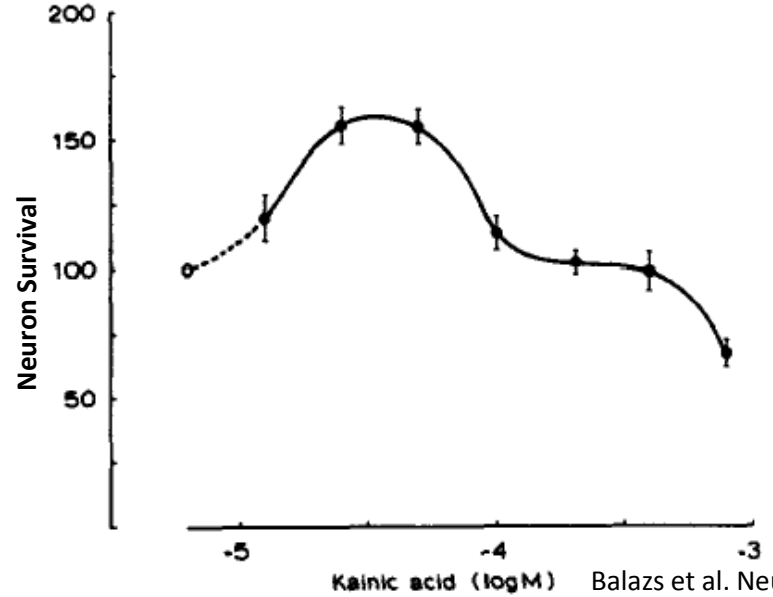
'The sands of time' by Kirsten Lee, inspired by the perspective on healthy brain aging in *Nature Reviews Neuroscience* (2012; 13:209-216) written by Stranahan and Mattson.



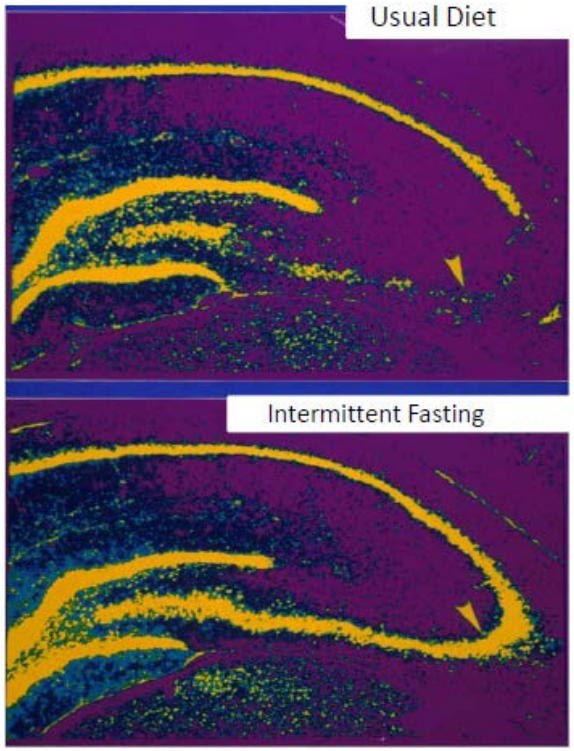


Kapogiannis and Mattson, Lancet Neurology; 2011; 10: 187-98.

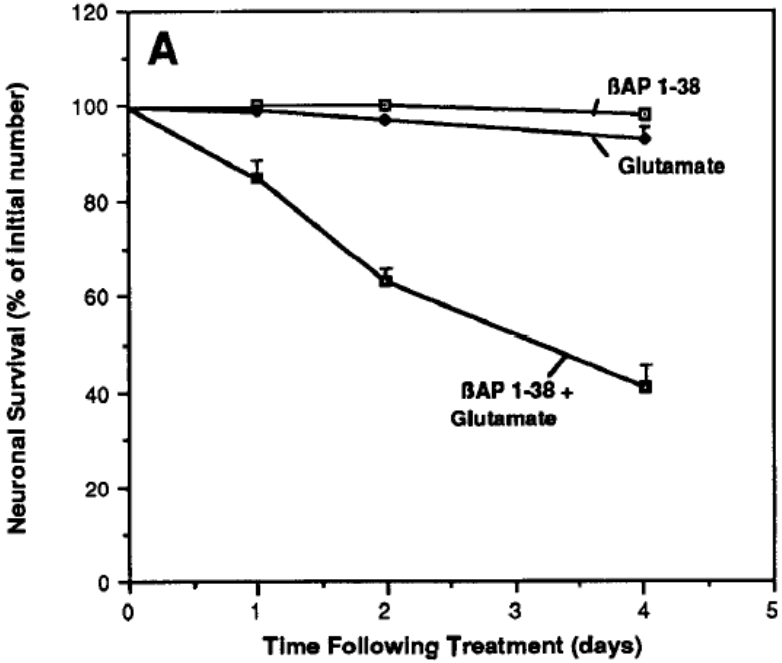




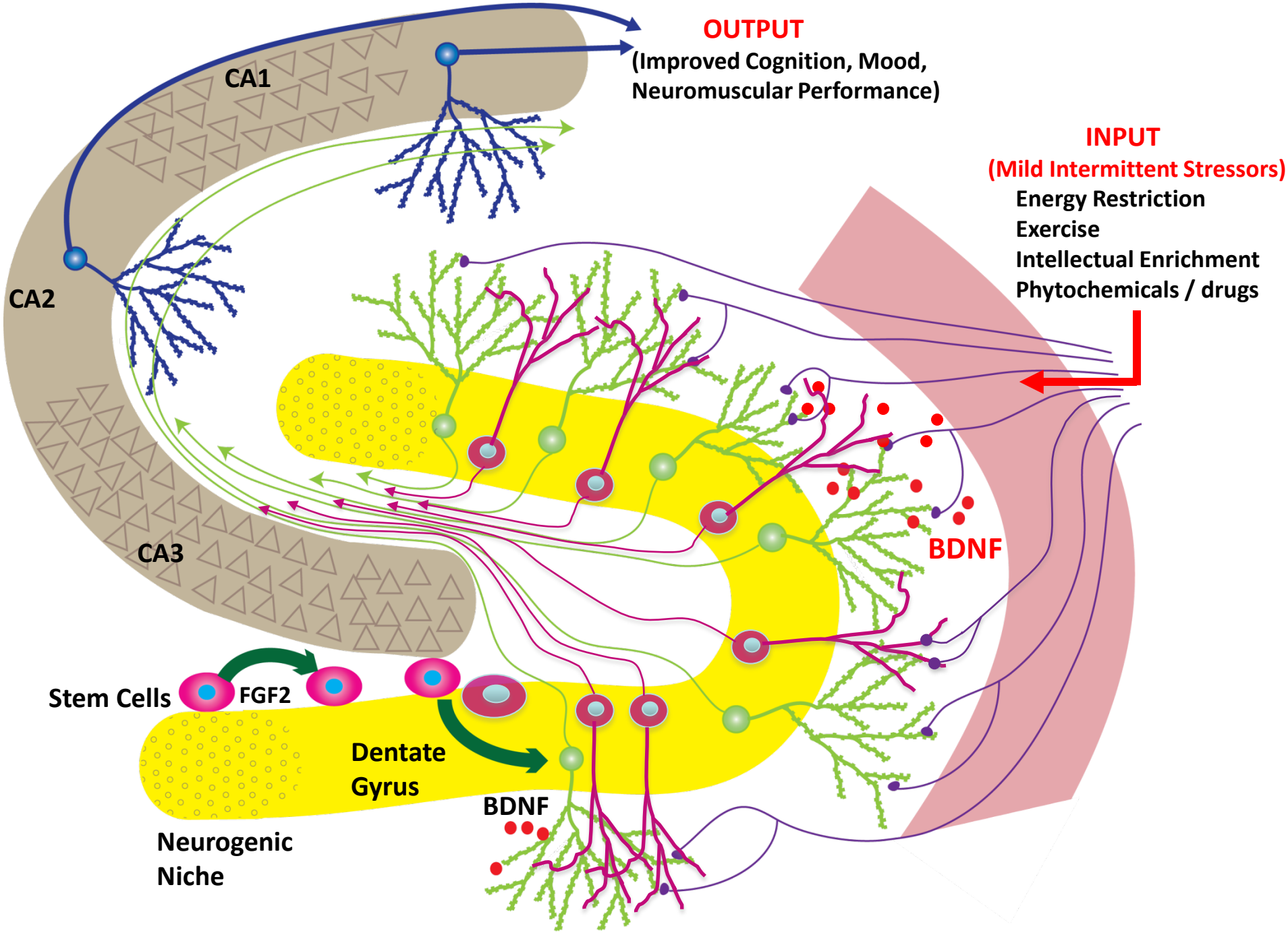
Balazs et al. Neuroscience 1990; 37:251-8.

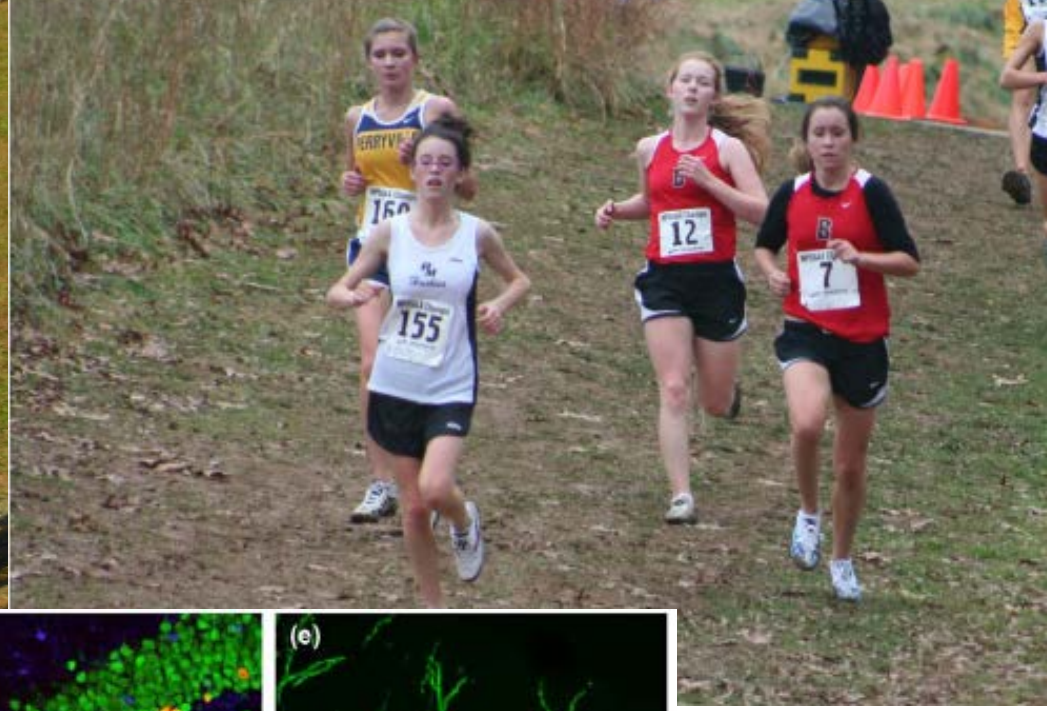


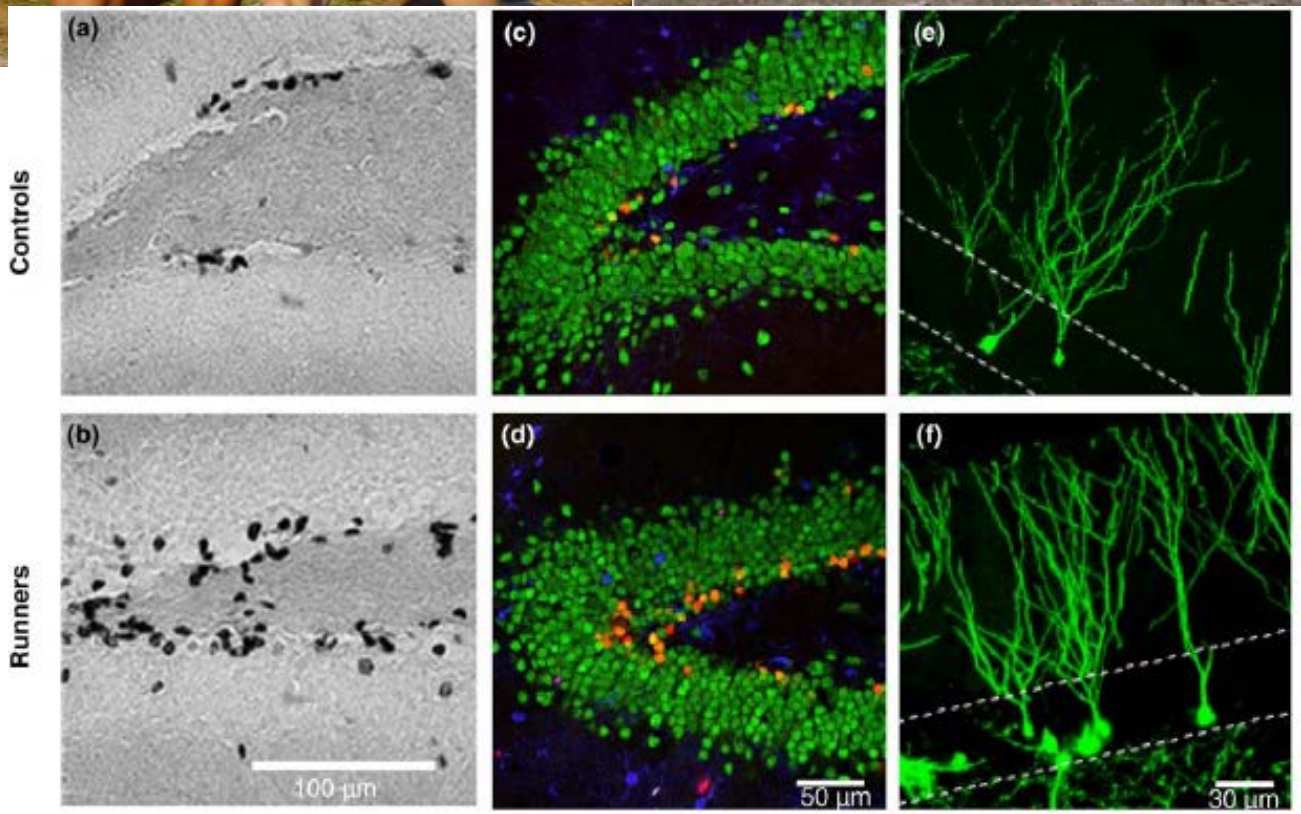
Bruce-Keller et al. *Ann. Neurol.* 45: 8-15.



Mattson et al. J Neurosci. 1992; 12:376-89.


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

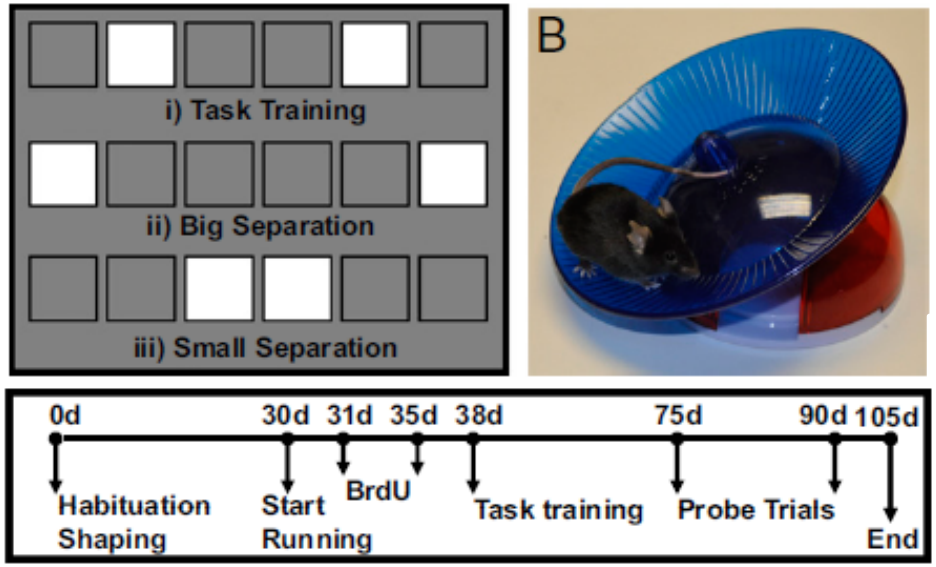


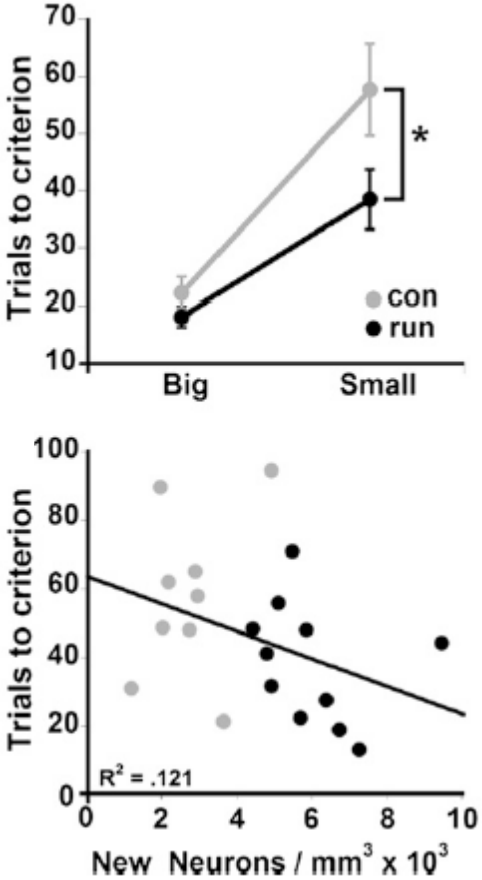


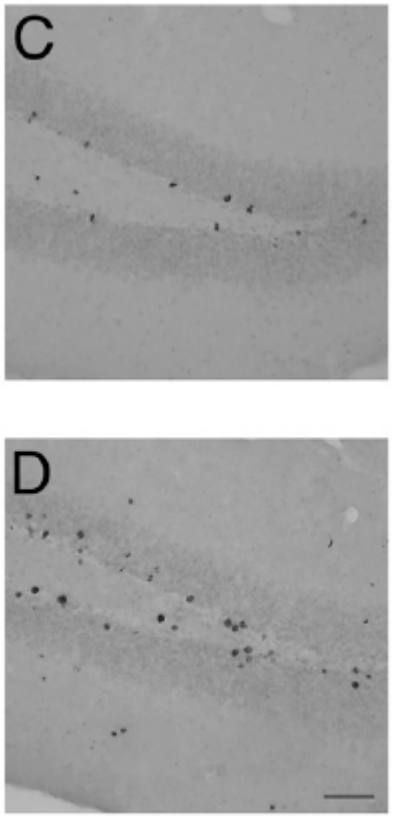
Henriette
Van Praag

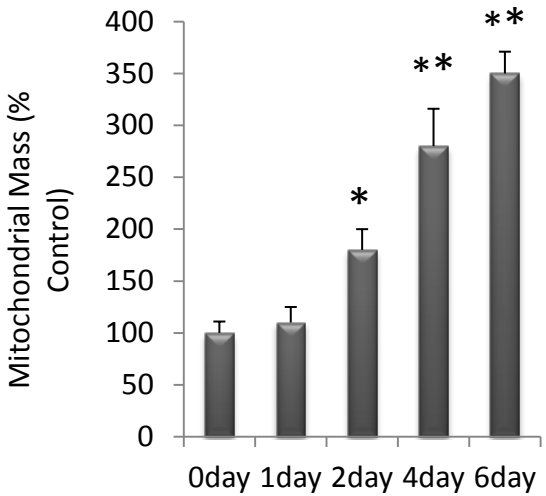
Running enhances spatial pattern separation in mice

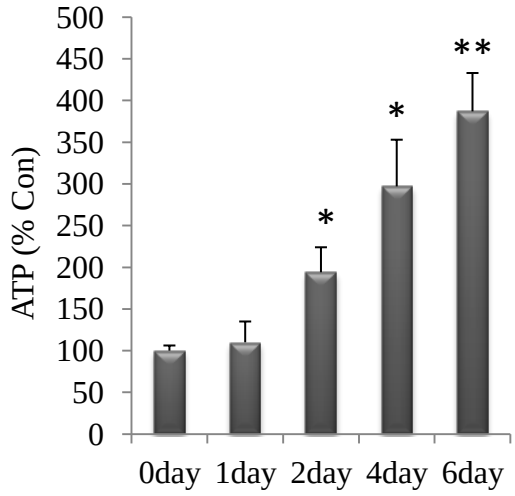
Creer DJ, Romberg C, Saksida LM, van Praag H, Bussey TJ. *Proc Natl Acad Sci U S A.* 2010; 107:2367-72.

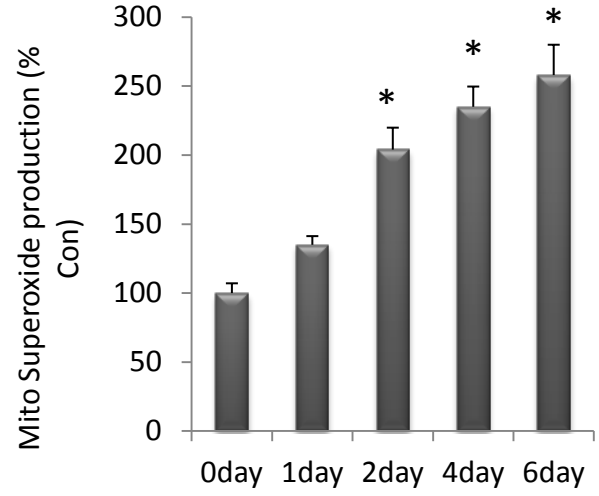


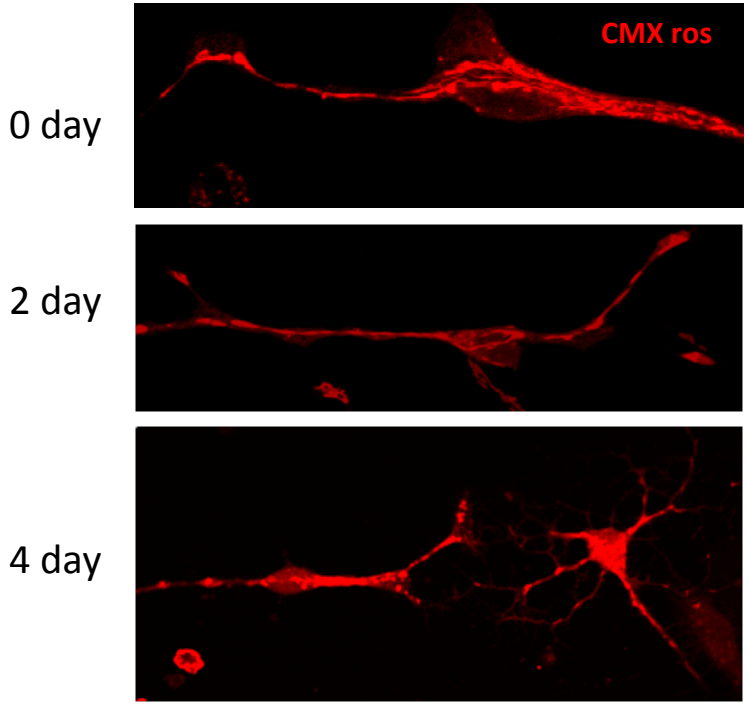


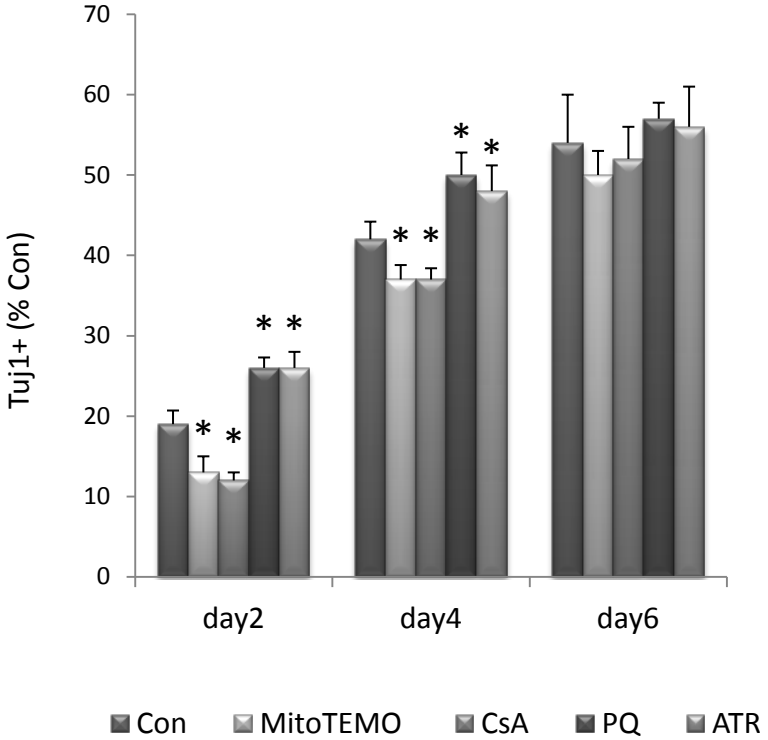


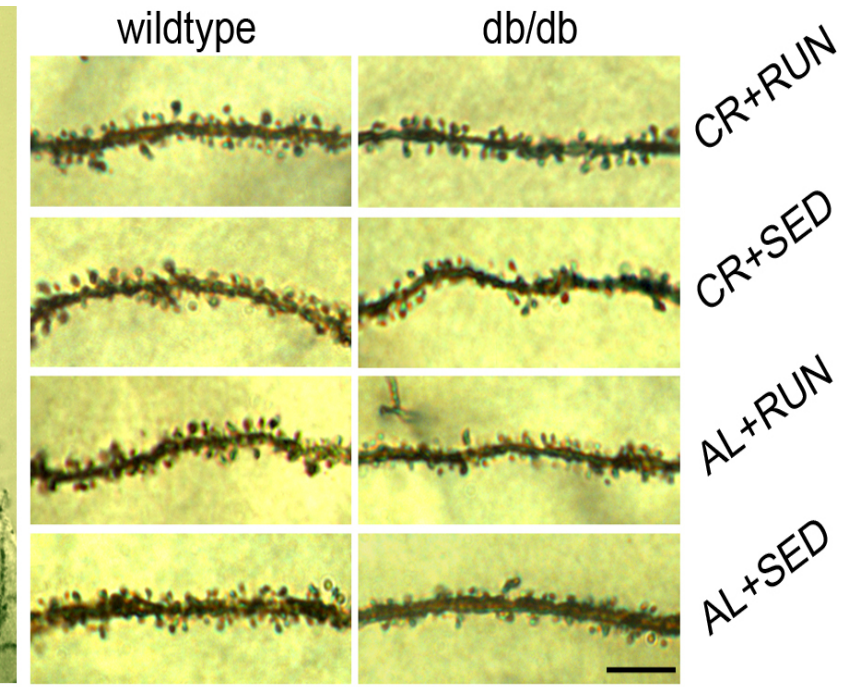

Mitochondrial Mass (% Control)
400
350
300
250
200
150
100
50
0
*
**
**
0day 1day 2day 4day 6day

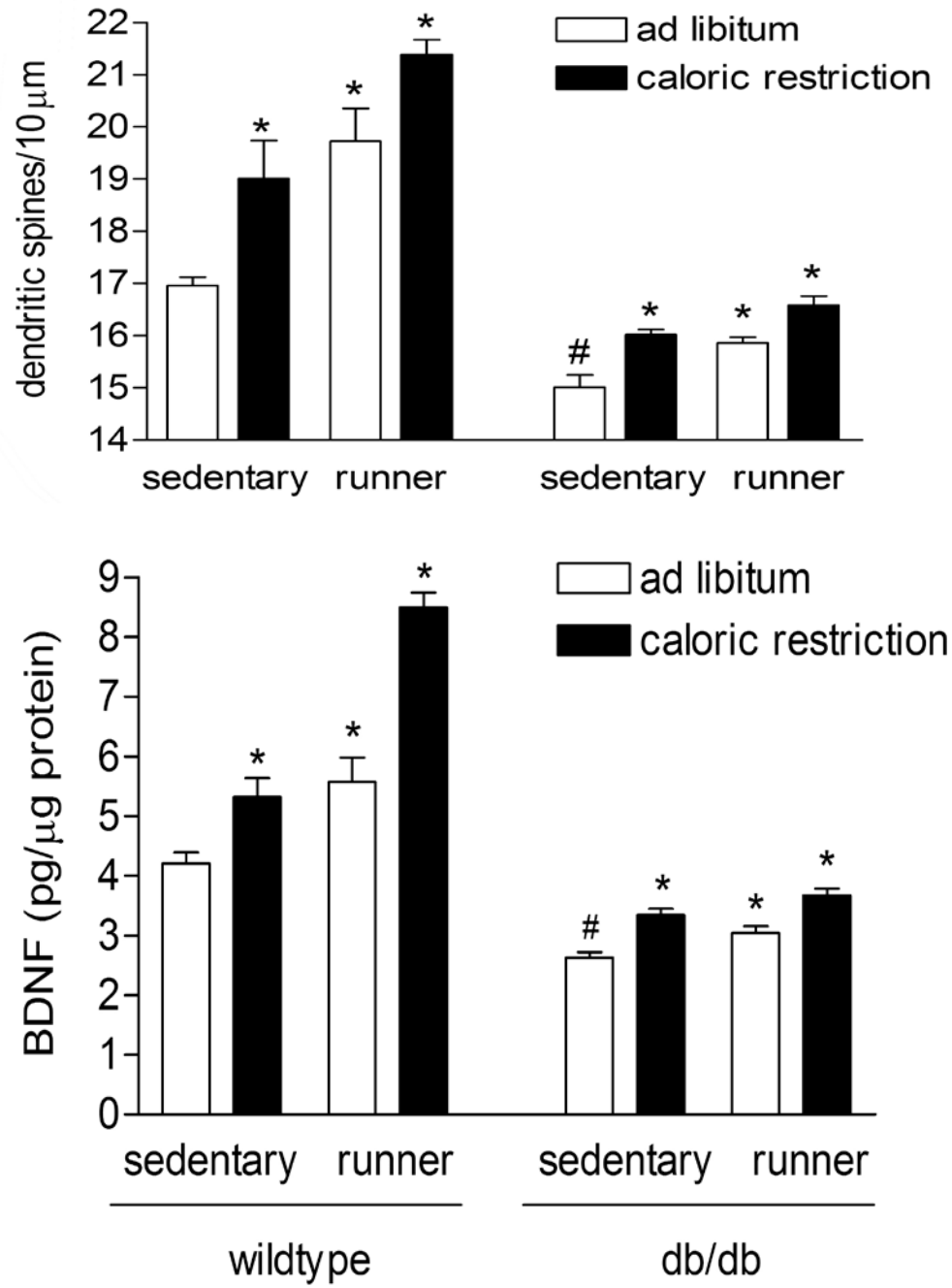

ATP (% Con)
500
450
400
350
300
250
200
150
100
50
0
*
*
**
0day 1day 2day 4day 6day


Mito Superoxide production (% Con)
300
250
200
150
100
50
0
*
*
*
0day 1day 2day 4day 6day

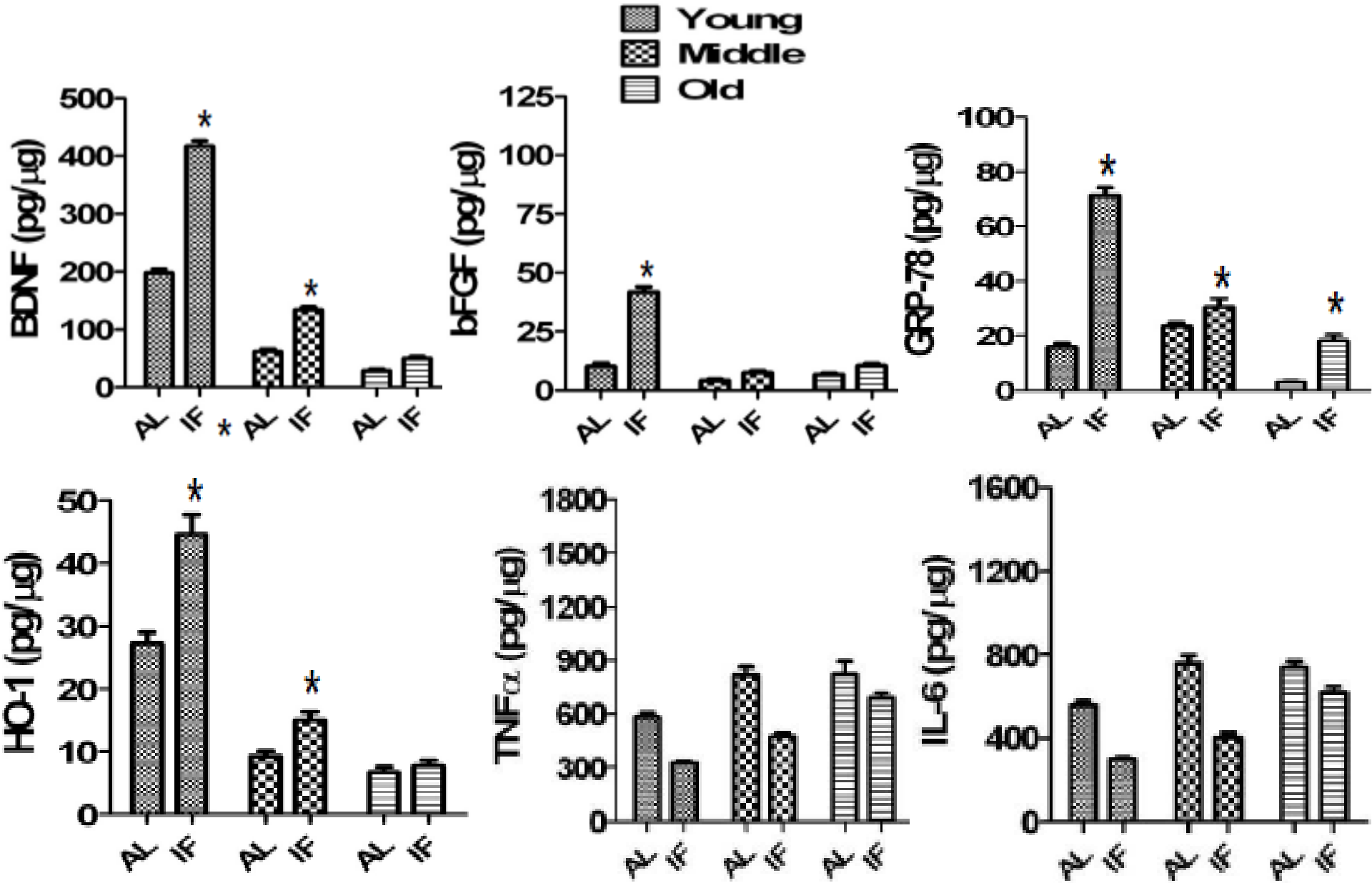

CMX ros
0 day
2 day
4 day


Tuj1+ (% Con)
70
60
50
40
30
20
10
0
day2
day4
day6
Con
MitoTEMO
CsA
PQ
ATR



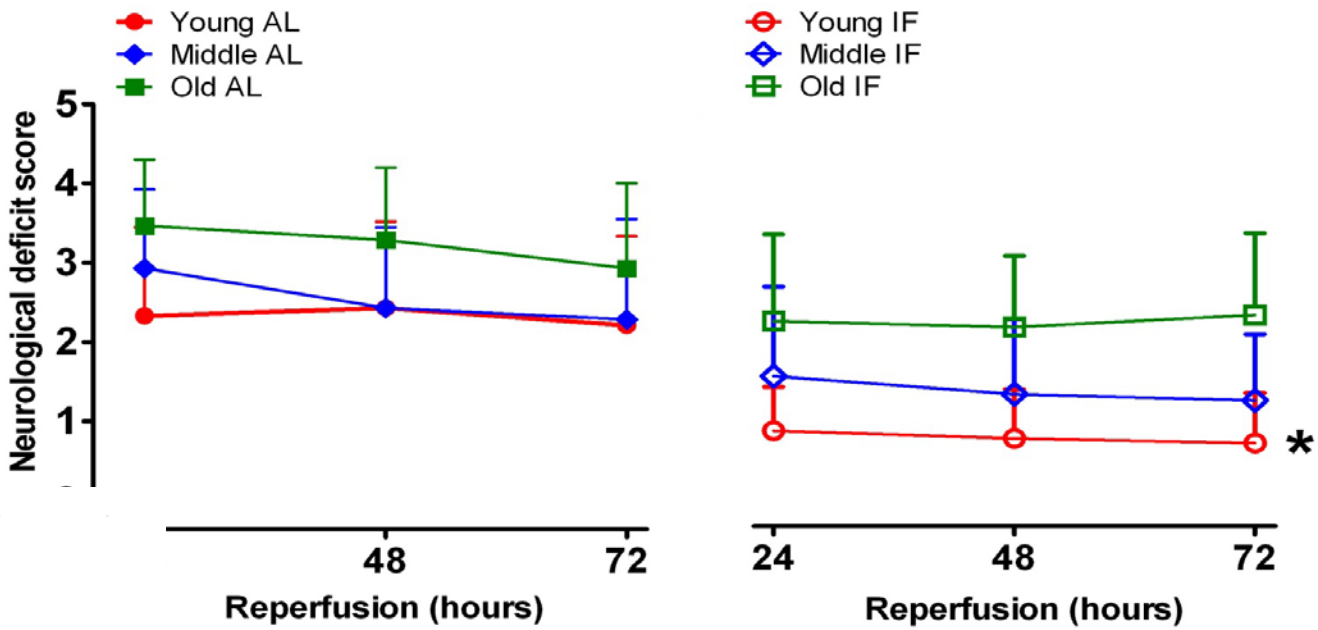


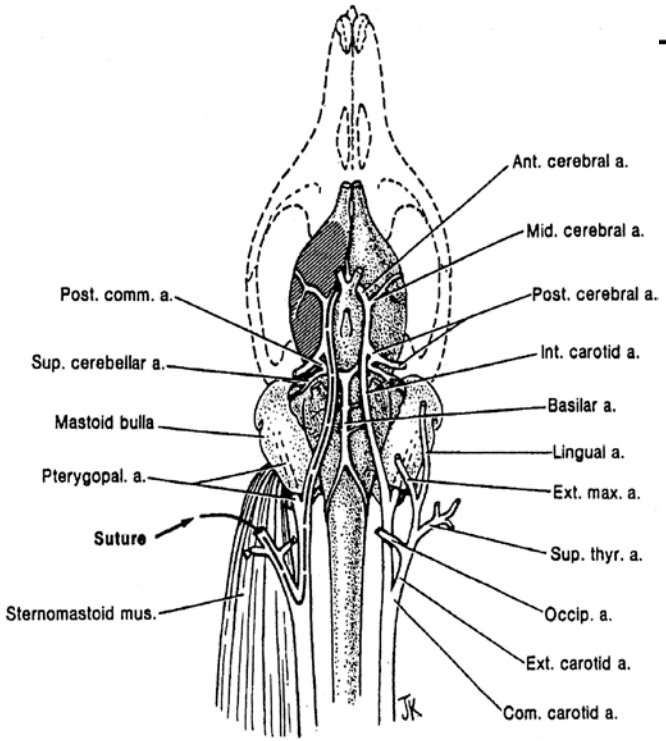
Stranahan et al. (2008) *Nature Neurosci.* 11:309-317 .
Stranahan et al. (2009) *Hippocampus* 19: 951-961.

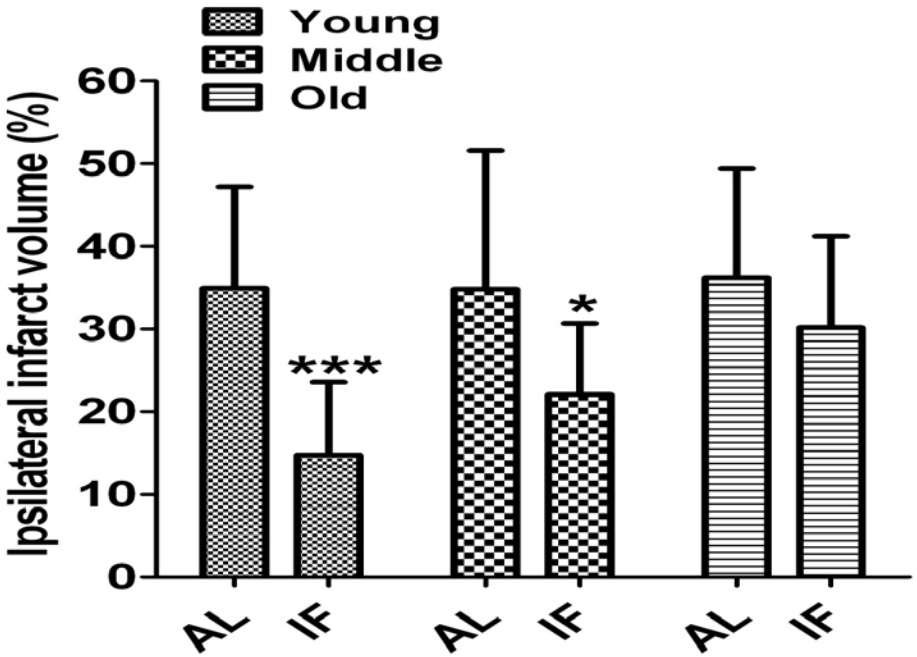


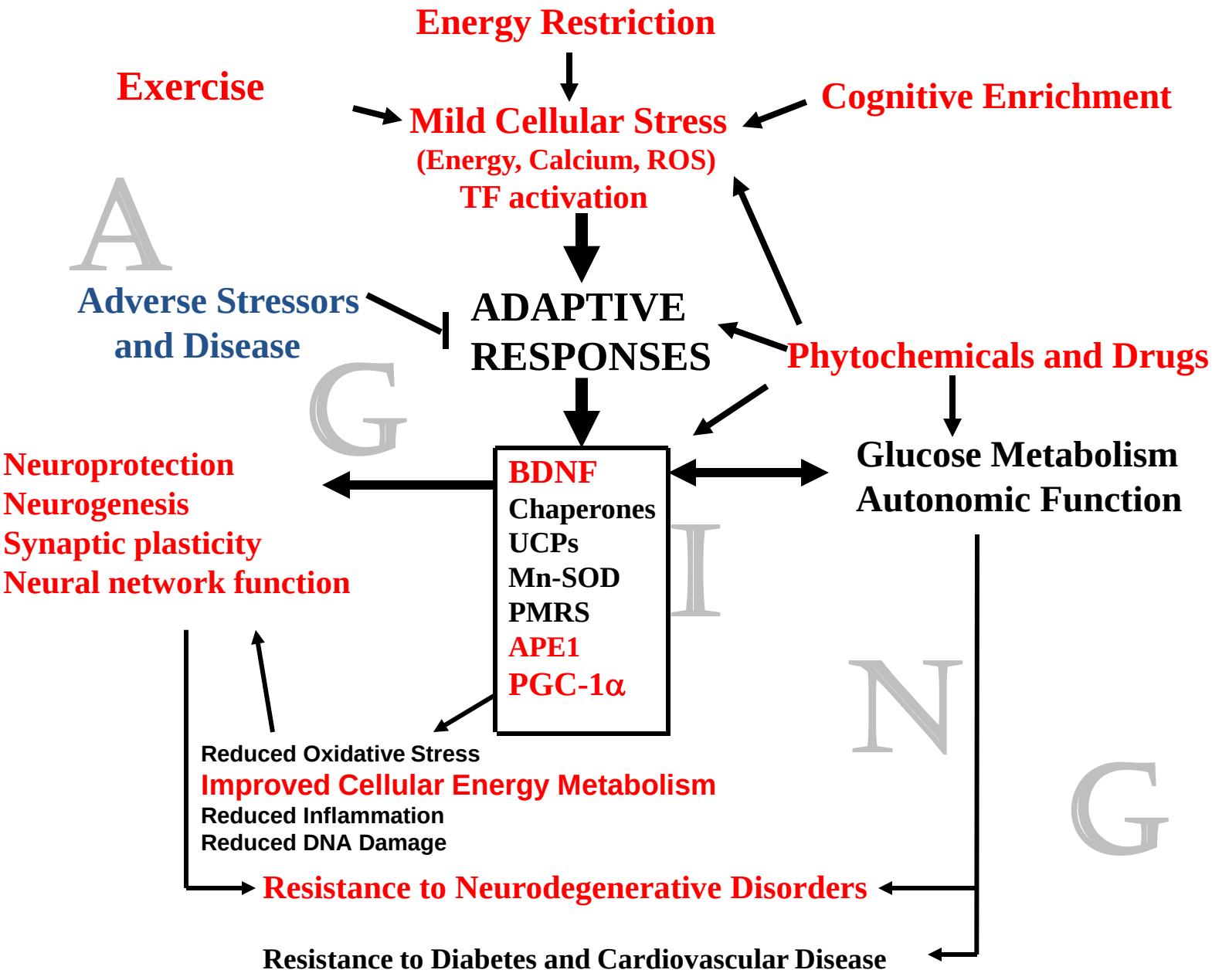
Arumugam, T. V. et al. (2009) Age and energy intake interact to modify cell stress pathways and stroke outcome. *Ann. Neurol.* 67(1):41-52.

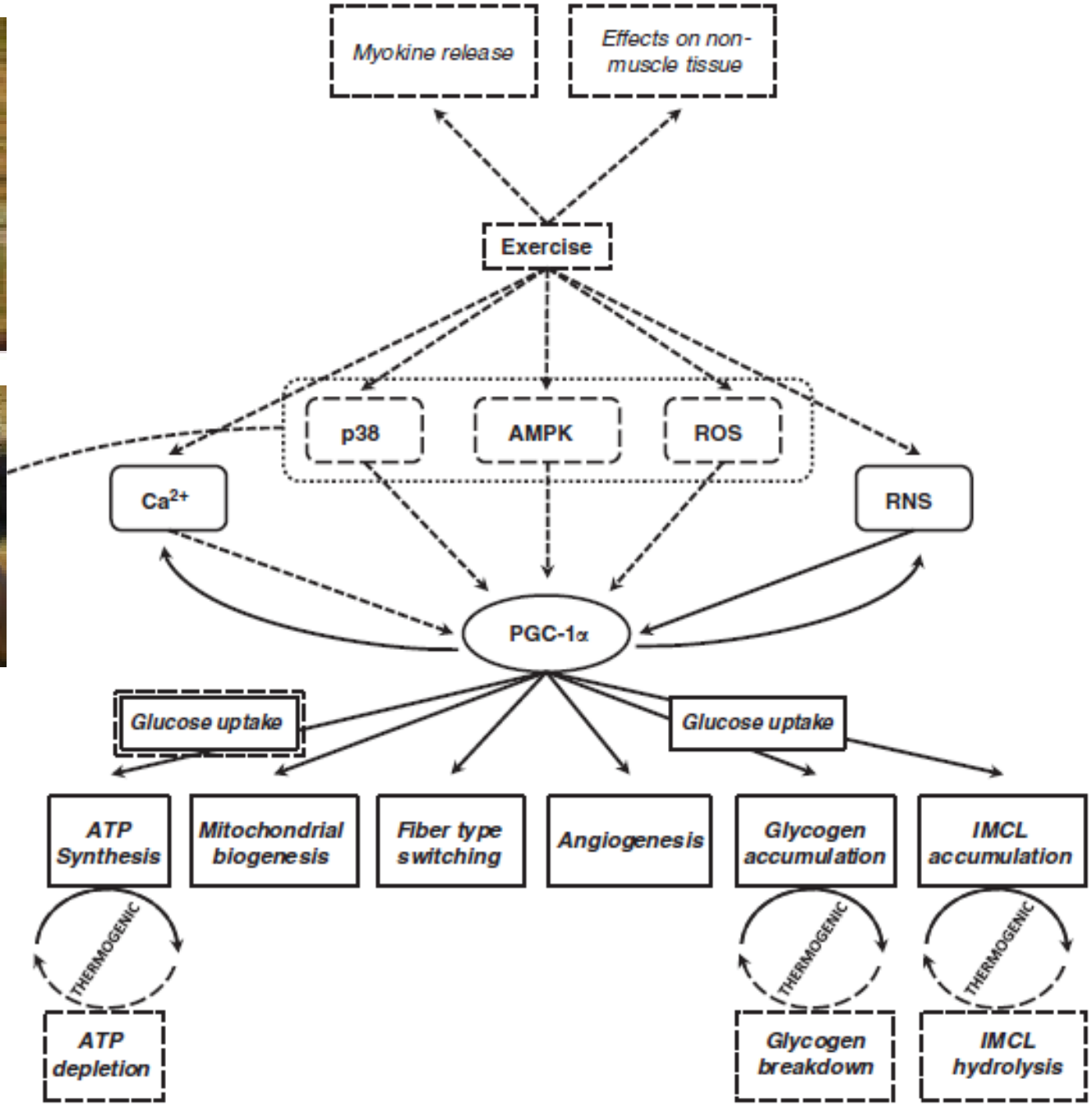
Arumugam, T. V. et al. (2009) Age and energy intake interact to modify cell stress pathways and stroke outcome. *Ann. Neurol.* 67(1):41-52.





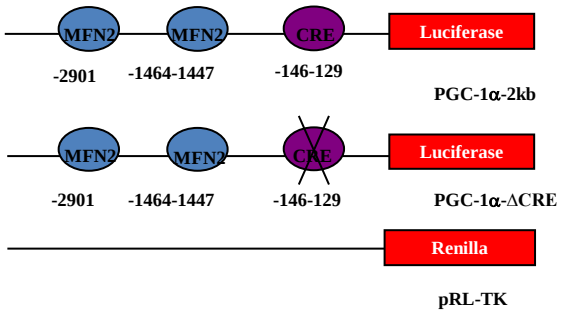


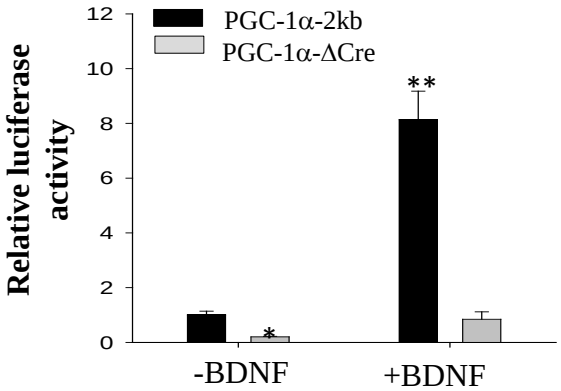

Energy Restriction
Exercise
Cognitive Enrichment
Mild Cellular Stress
(Energy, Calcium, ROS)
TF activation
A
Adverse Stressors
and Disease
ADAPTIVE
RESPONSES
Phytochemicals and Drugs
G
Neuroprotection
Neurogenesis
Synaptic plasticity
Neural network function
BDNF
Chaperones
UCPs
Mn-SOD
PMRS
APE1
PGC-1α
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

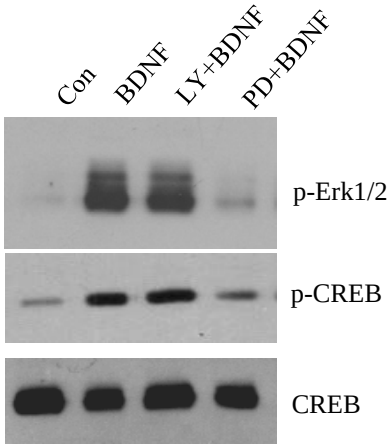


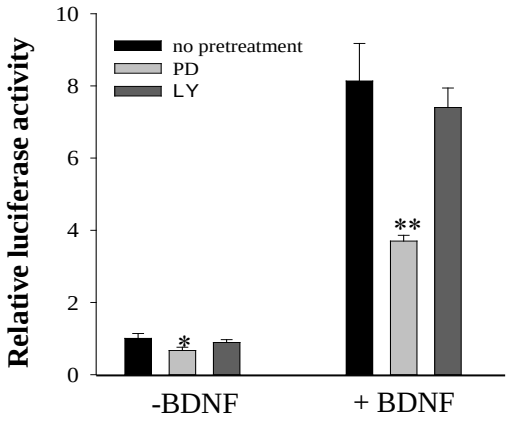
Summermatter and Handschin, 2012

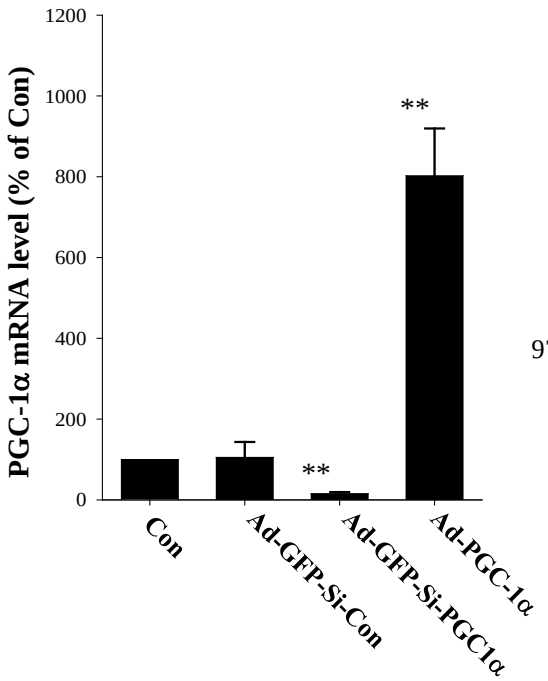
Cheng A et al. (2012) Involvement of PGC-1α in the formation and maintenance of neuronal dendritic spines. *Nature Commun.* In pr2012 Dec 4;3:1250.

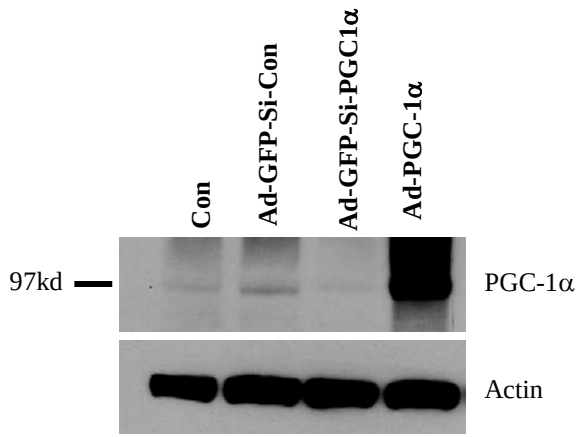


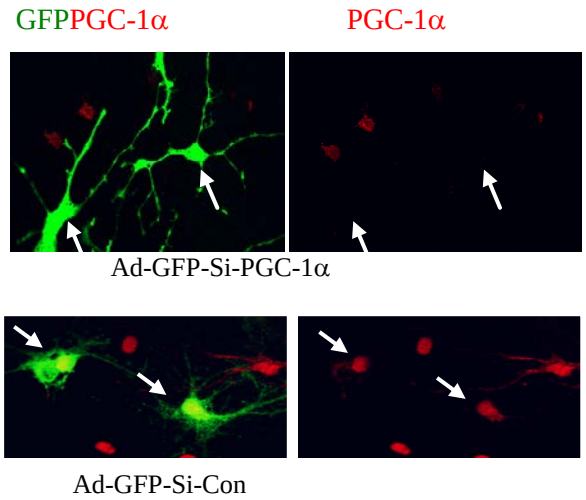


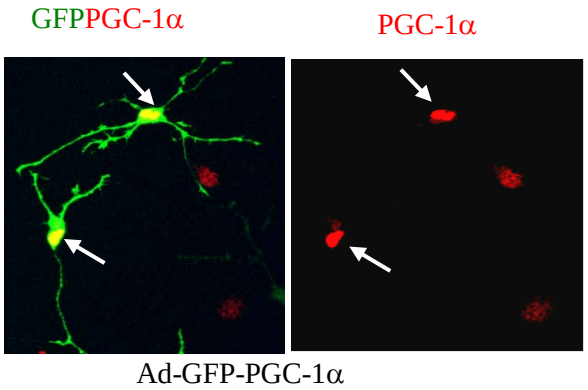


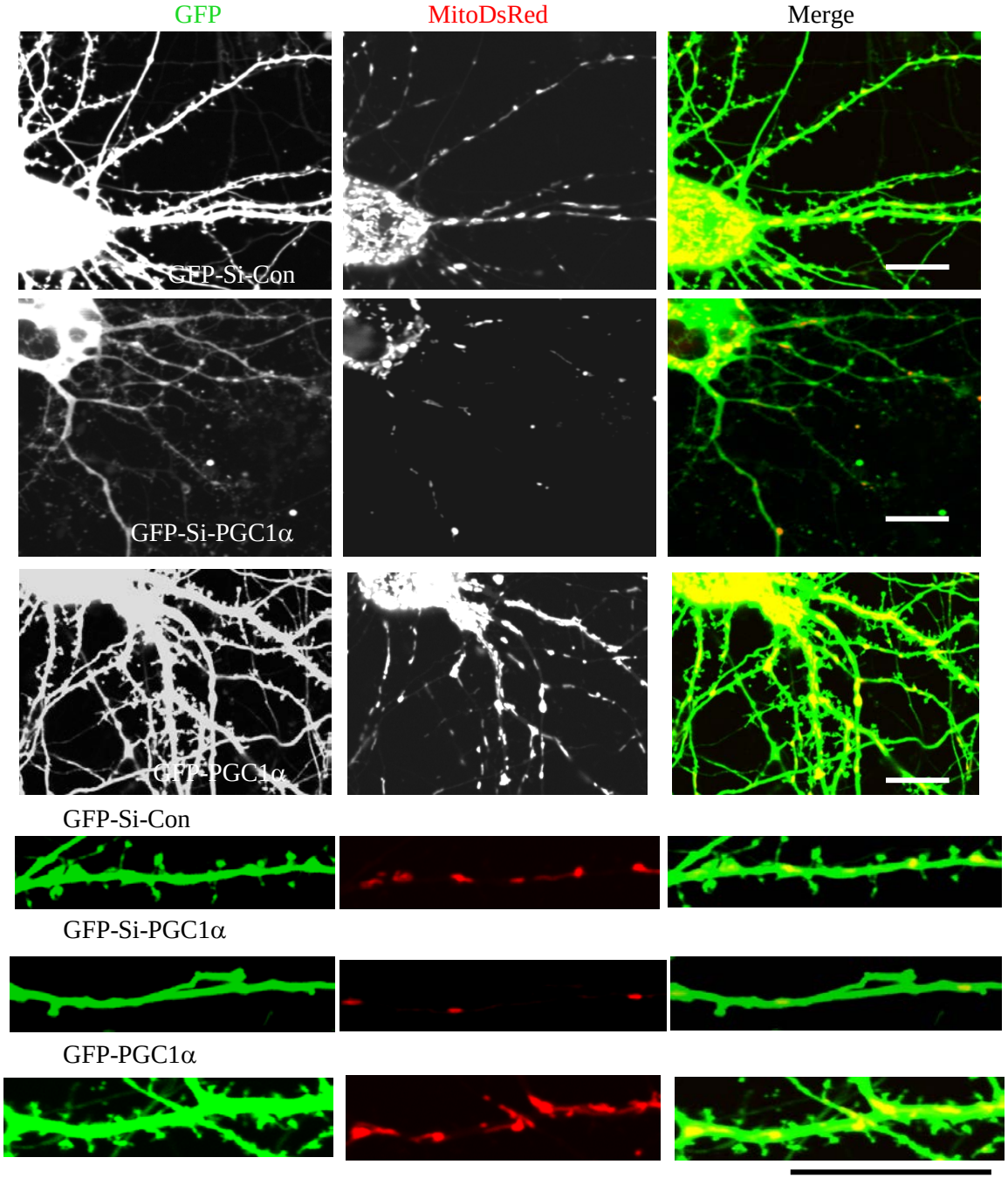


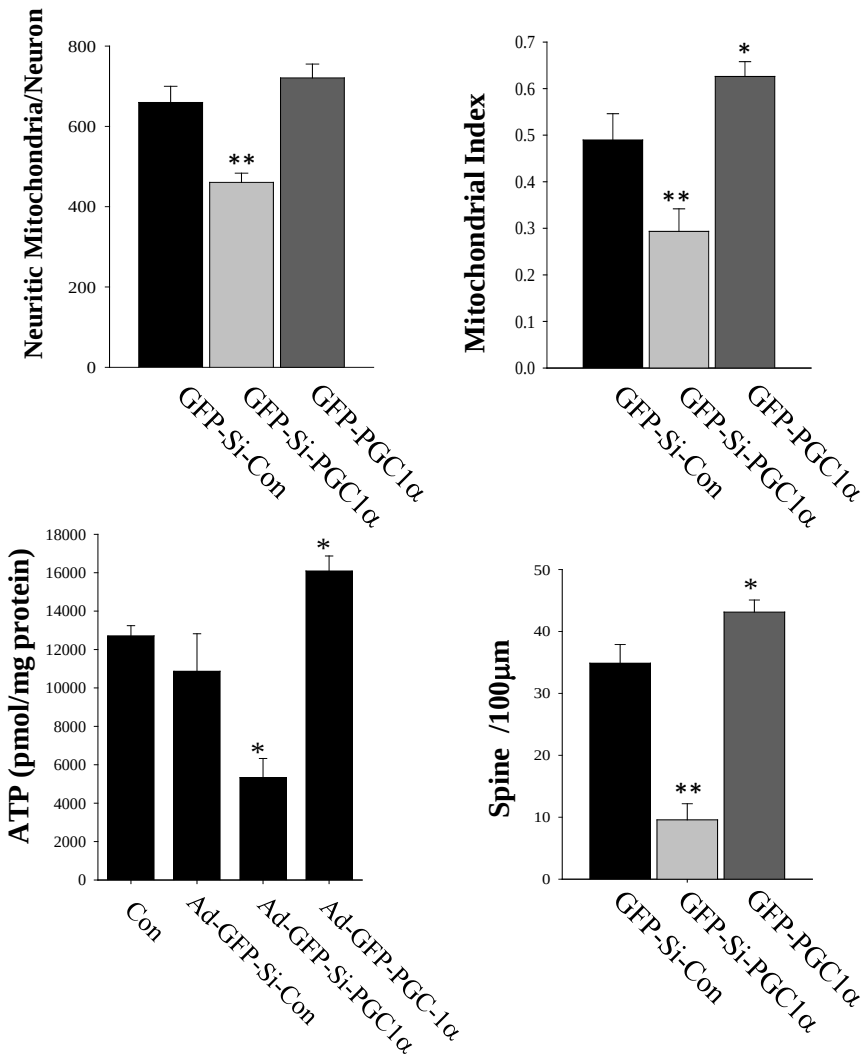

PGC-1α mRNA level (% of Con)
1200
1000
800
600
400
200
0
**
**
Con
Ad-GFP-Si-Con
Ad-GFP-Si-PGC1α
Ad-PGC-1α


Con
Ad-GFP-Si-Con
Ad-GFP-Si-PGC1α
Ad-PGC-1α
97kd
PGC-1α
Actin

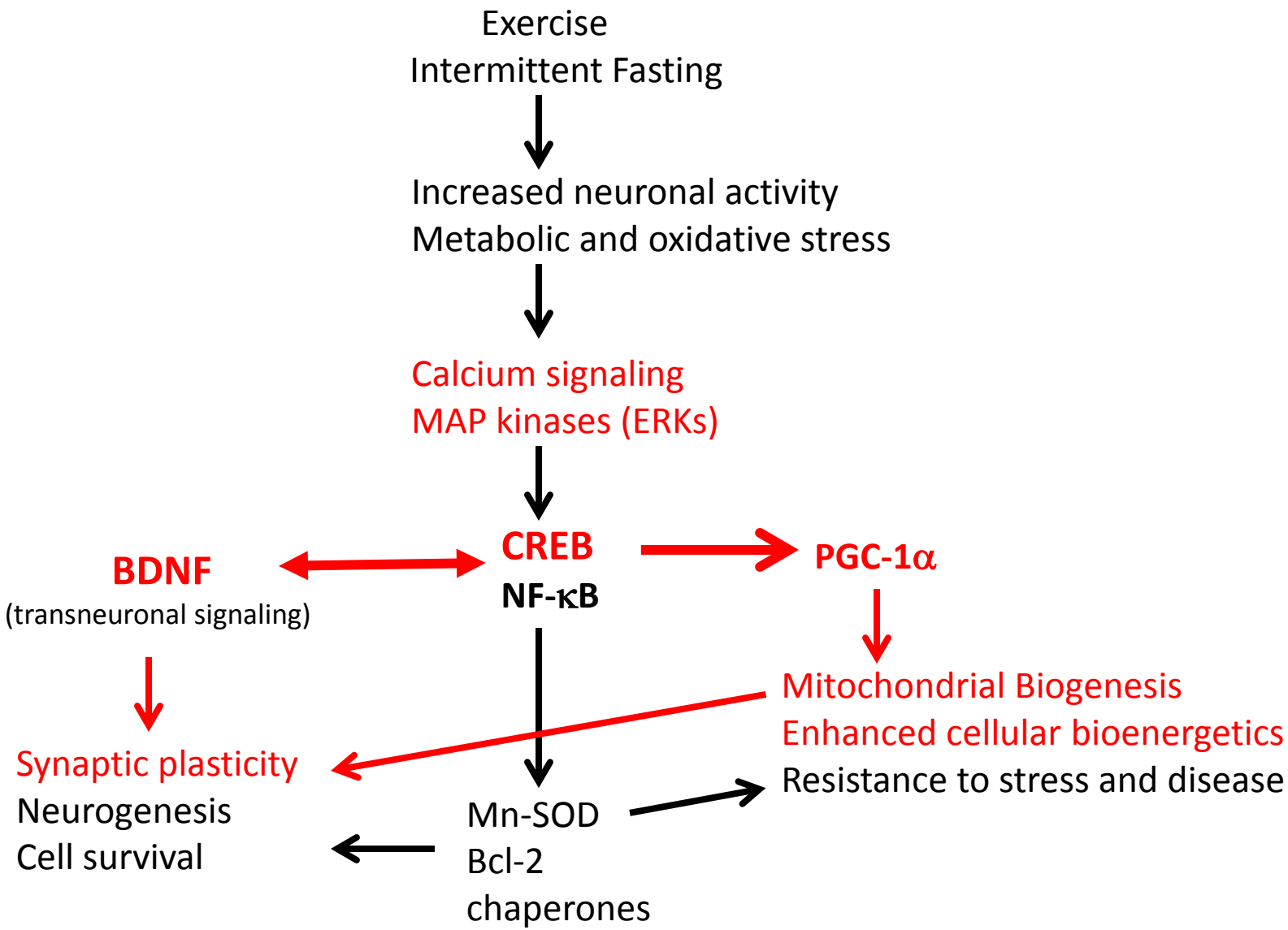

GFPPGC-1α
PGC-1α
Ad-GFP-Si-PGC-1α
Ad-GFP-Si-Con

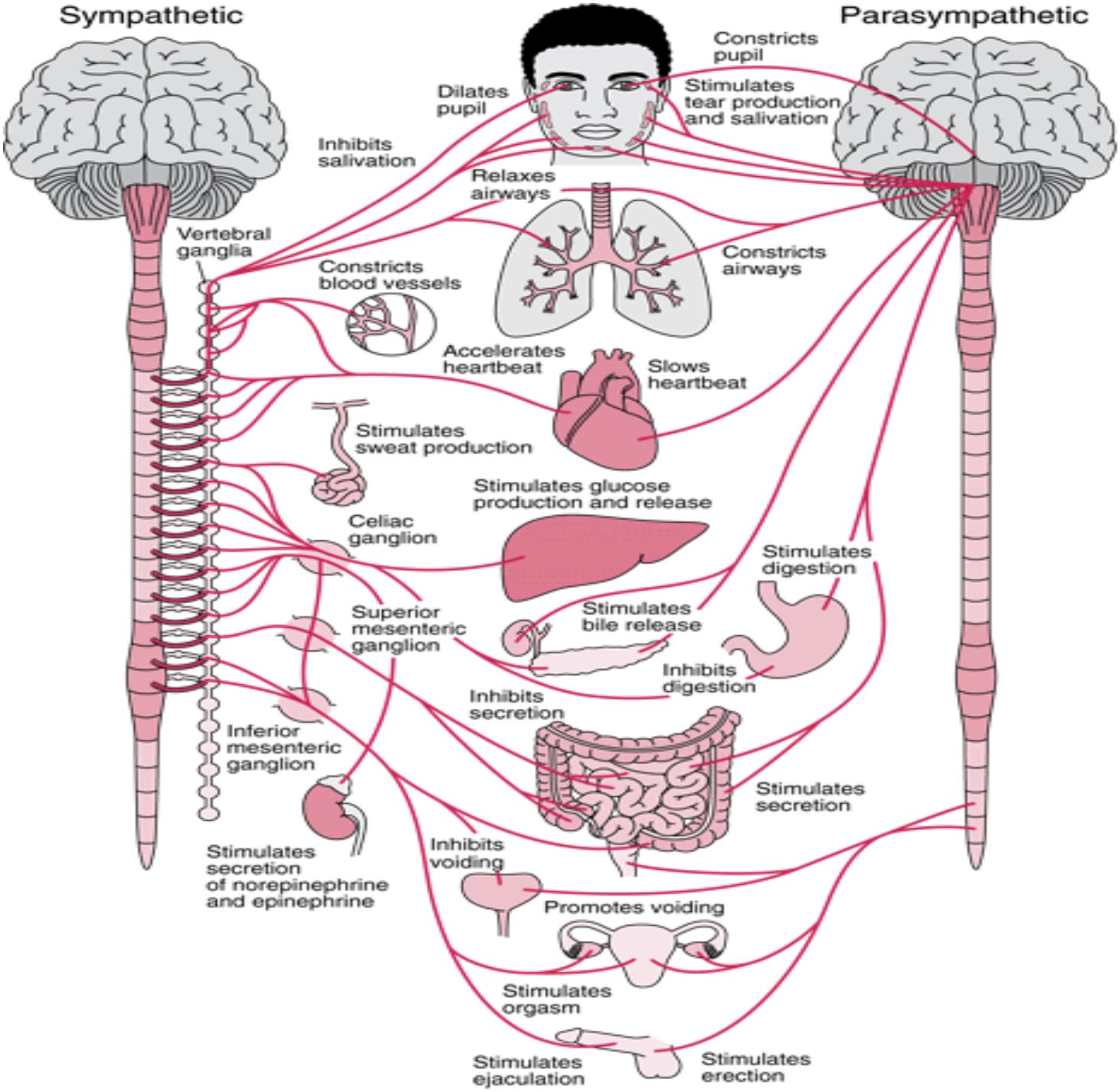

GFPPGC-1α
PGC-1α
Ad-GFP-PGC-1α


GFP
MitoDsRed
Merge
GFP-Si-Con
GFP-Si-PGC1α
GFP-PGC1α
GFP-Si-Con
GFP-Si-PGC1α
GFP-PGC1α


Neuritic Mitochondria/Neuron
800
600
400
200
0
**
GFP-Si-Con
GFP-Si-PGC1α
GFP-PGC1α
Mitochondrial Index
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
*
**
GFP-Si-Con
GFP-Si-PGC1α
GFP-PGC1α
ATP (pmol/mg protein)
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
*
*
Con
Ad-GFP-Si-Con
Ad-GFP-Si-PGC1α
Ad-GFP-PGC-1α
Spine /100μm
50
40
30
20
10
0
*
**
GFP-Si-Con
GFP-Si-PGC1α
GFP-PGC1α

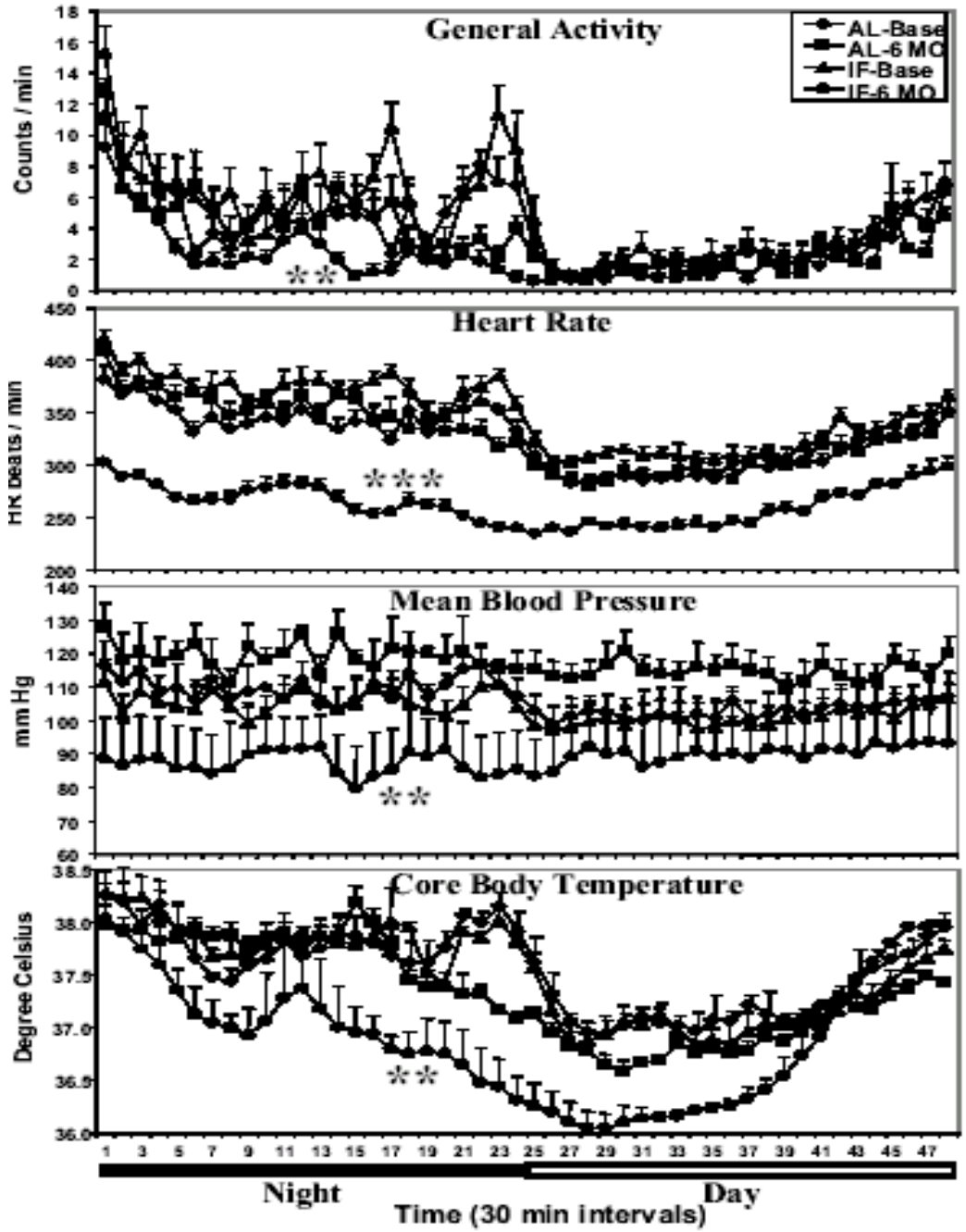
Cheng A, Wan R, Yang JL, Kamimura N, Son TG, Ouyang X, Luo Y, Okun E, Mattson MP. (2012) Involvement of PGC-1α in the formation and maintenance of neuronal dendritic spines. *Nature Commun.* 2012;3:1250. doi: 10.1038/ncomms2238.

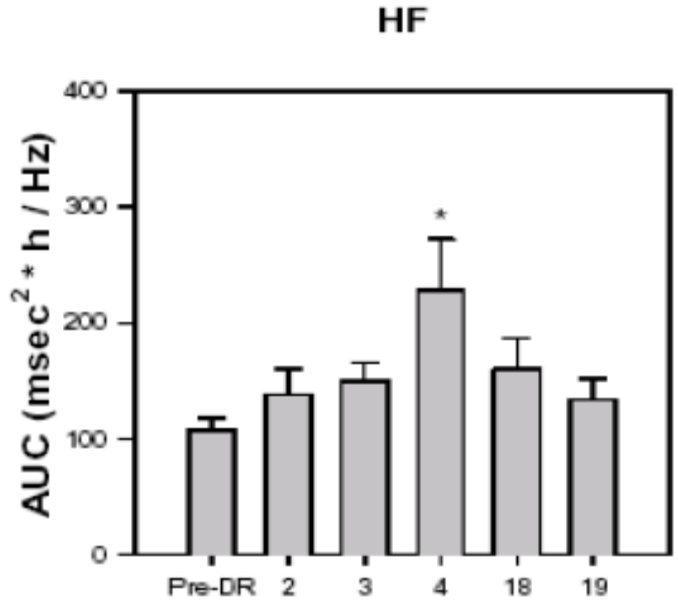


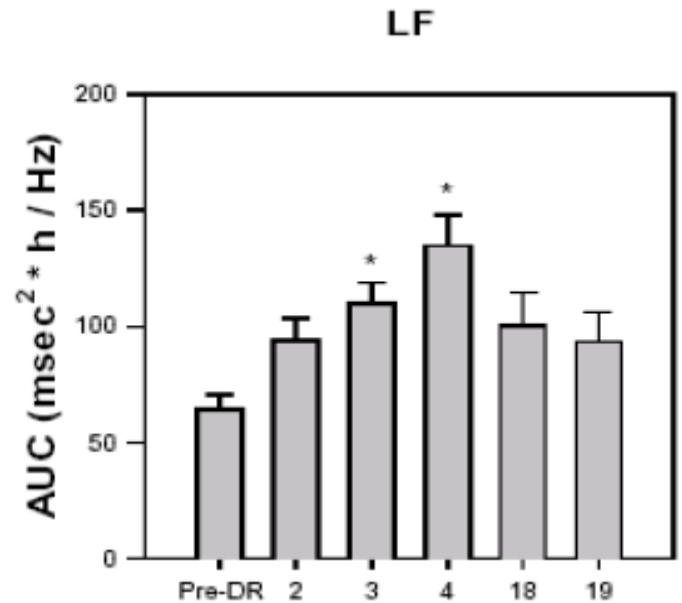


Merck Manual

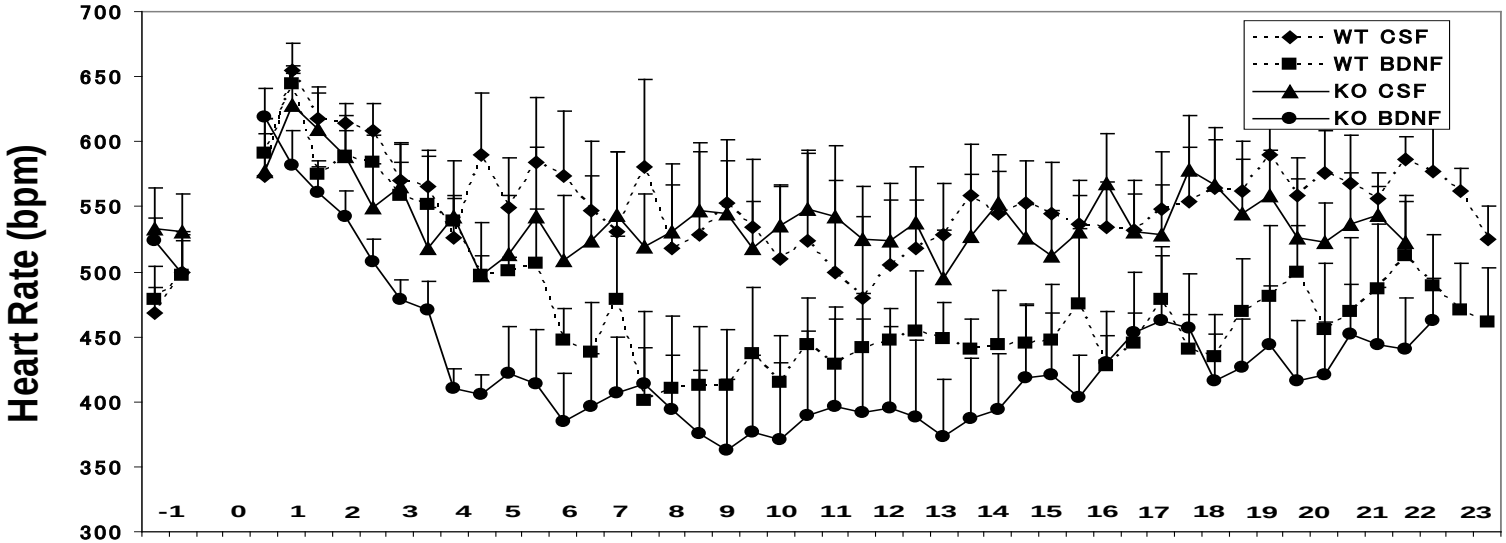
Intermittent fasting reduces resting heart rate and blood pressure, and increases heart rate variability in rats

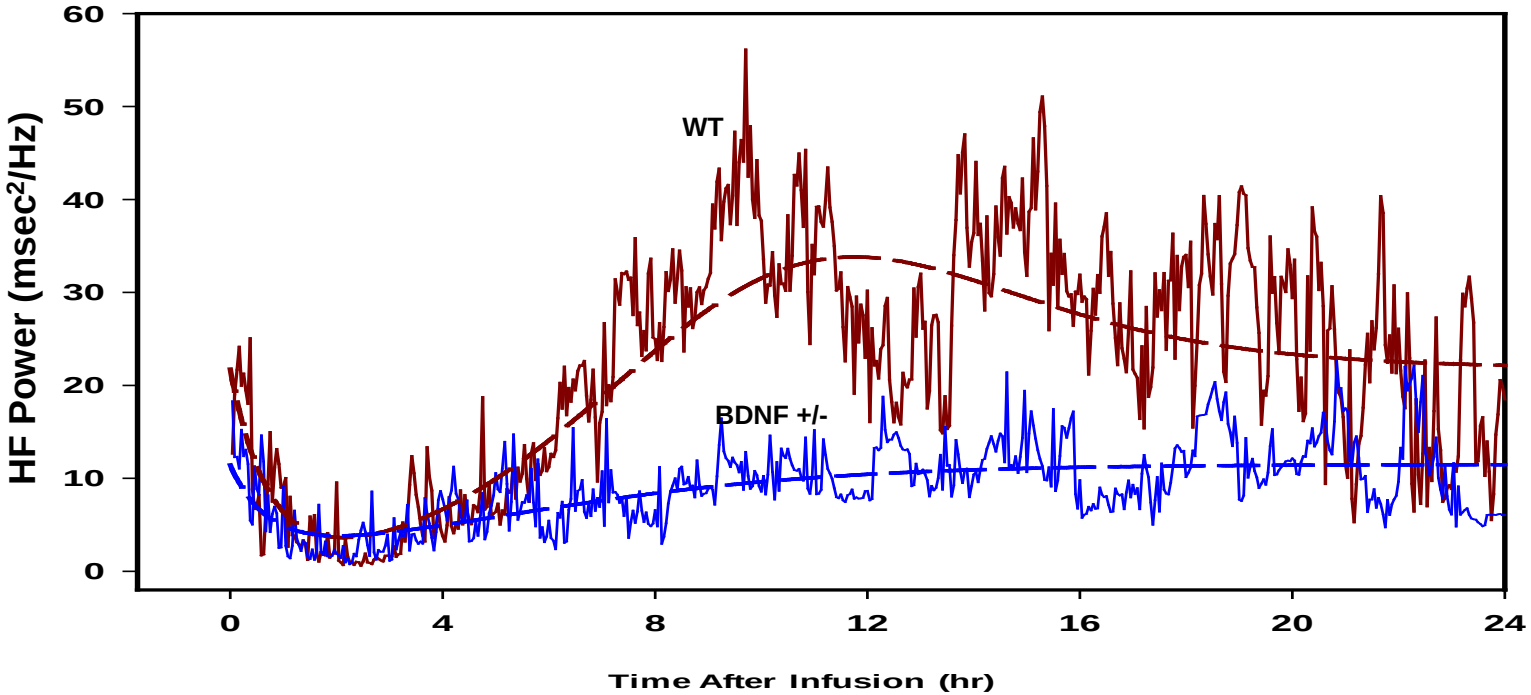






Brainstem BDNF reduces resting heart rate and increases heart rate variability in mice

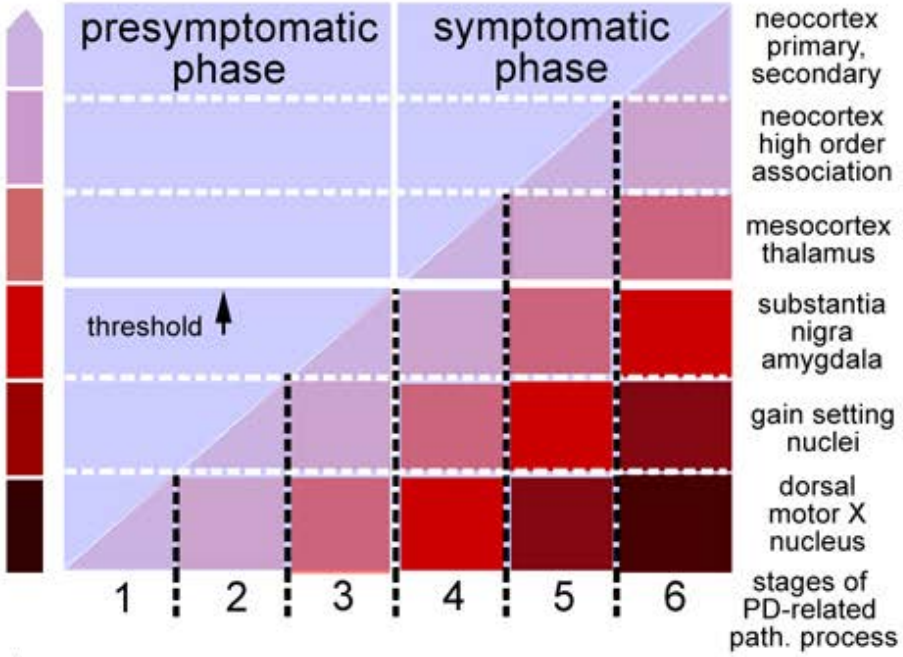


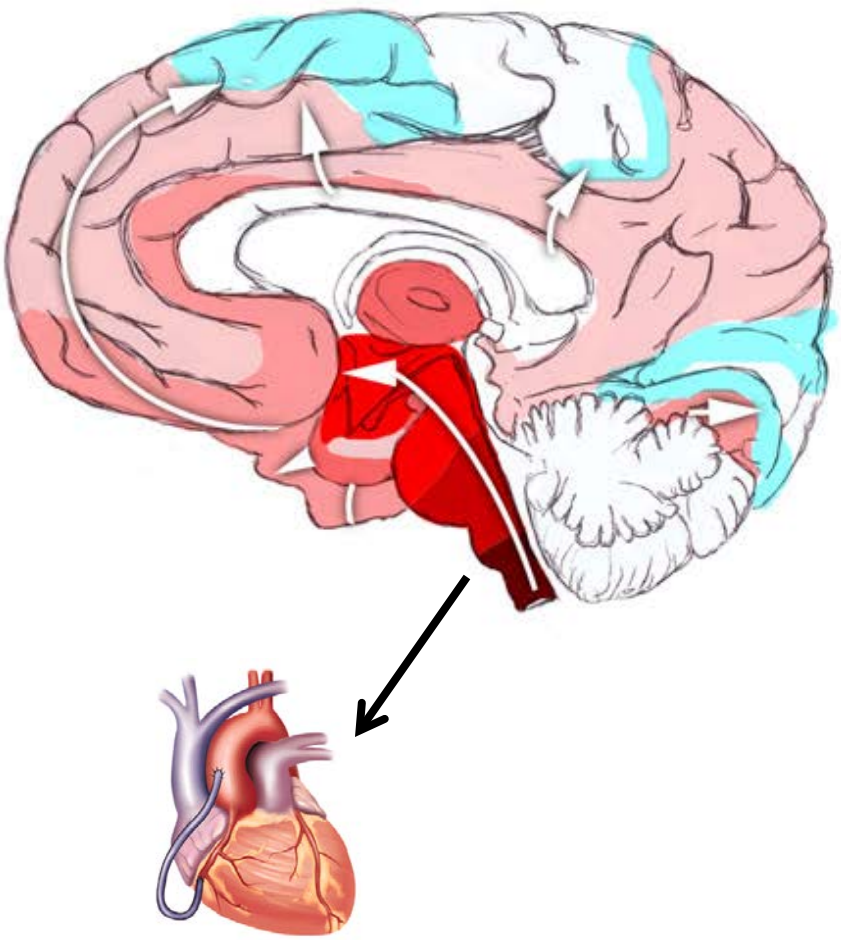


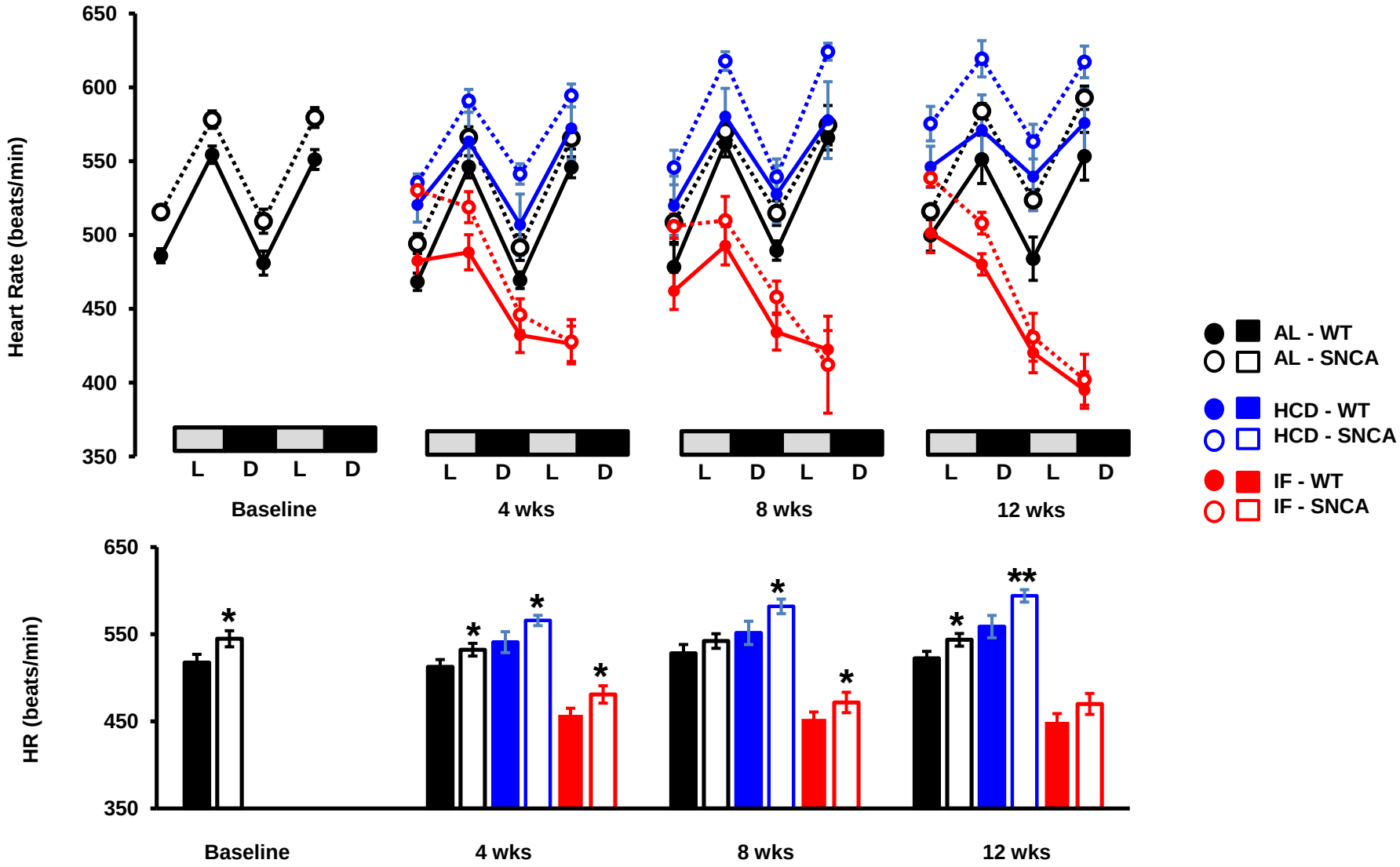
Autonomic Nervous System Dysfunction Precedes Motor Symptoms in PD.

Brainstem Pathology Precedes Substantia Nigra Pathology in PD.

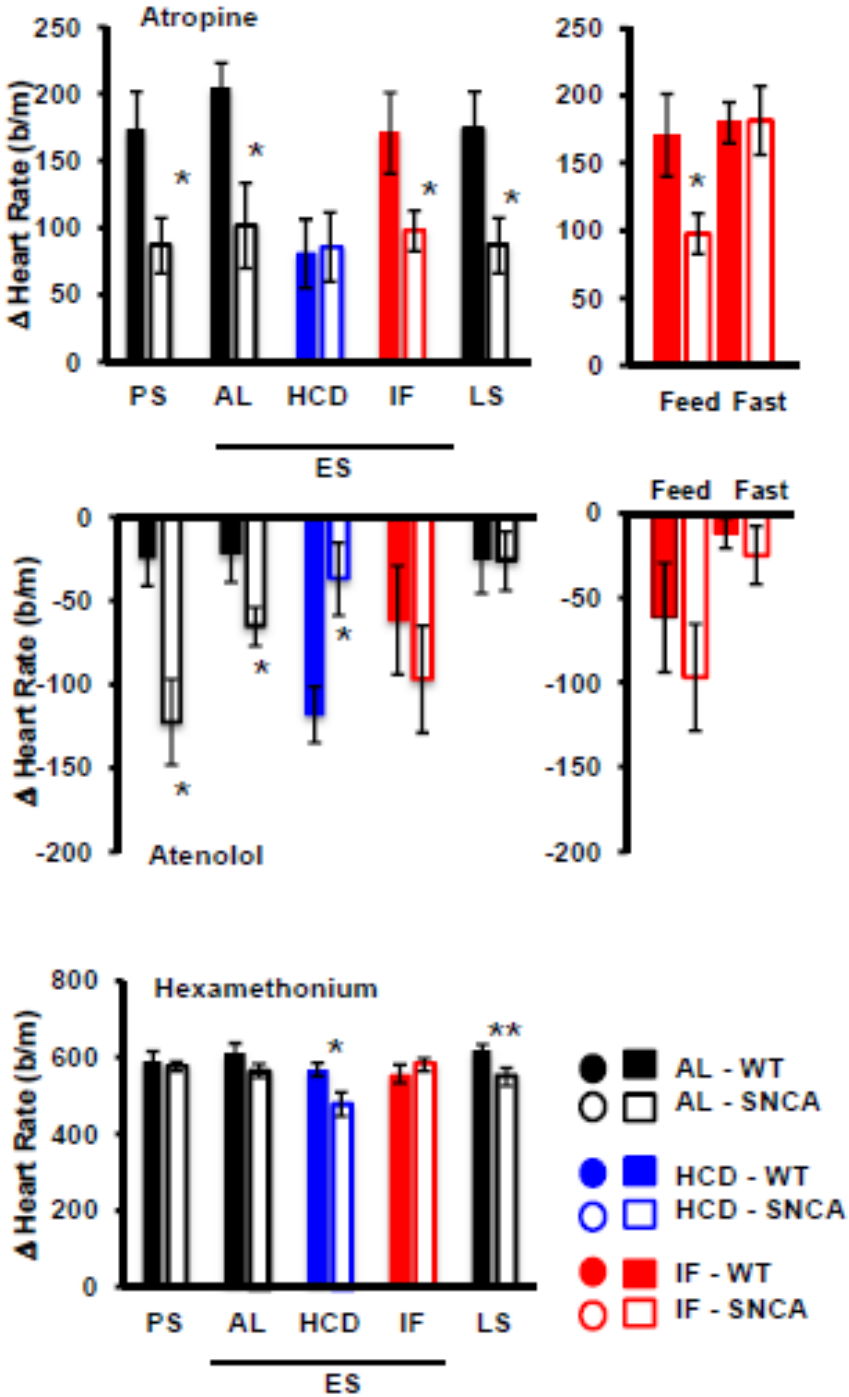
(Braak et al.; 2004; Cell Tissue Research)







Dietary energy intake modifies brainstem autonomic dysfunction caused by mutant α-synuclein.
Griffioen KJ, Rothman SM, Ladenheim B, Wan R, Vranis N, Hutchison E, Okun E, Cadet JL, **Mattson MP**.
Neurobiol Aging. 2012 Aug 7. [Epub ahead of print]


Atropine
Δ Heart Rate (b/m)
250
200
150
100
50
0
PS
AL
HCD
IF
LS
ES
Feed
Fast
Atenolol
-50
-100
-150
-200
Hexamethonium
800
600
400
200
AL - WT
AL - SNCA
HCD - WT
HCD - SNCA
IF - WT
IF - SNCA

INTERMITTENT FASTING AND HEALTH: HUMAN STUDIES

Johnson, J. B., W. Summer, R. G. Cutler, B. Martin, D. H. Hyun, V. D. Dixit, M. Pearson, M. Nassar, S. Maudsley, O. Carlson, S. John, D. R. Laub and M. P. Mattson (2007) Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Rad. Biol. Med.* 42: 665-674.

Harvie, M. N., M. Pegington, M. P. Mattson, J. Frystyk, B. Dillon, G. Evans, J. Cuzick, S. Jebb, B. Martin, R. G. Cutler, T. G. Son, S. Maudsley, O. D. Carlson, J. M. Egan, A. Flyvbjerg and A. Howell (2010) The effects of intermittent and continuous energy restriction on weight loss, and metabolic disease risk markers: a randomized trial in young overweight women. *Int. J. Obesity.* 35: 714-727.

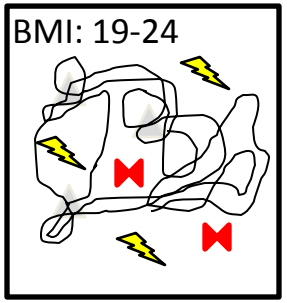
A TRIAL OF INTERMITTENT ENERGY RESTRICTION IN SUBJECTS AT RISK FOR COGNITIVE IMPAIRMENT. Mattson, Willette, Kapogianis et al.

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

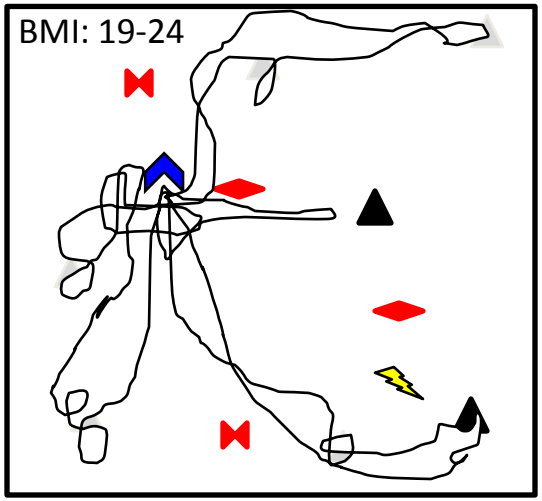
- Walking / running route
- Low energy density food
- High energy density food
- Predators and other hazards
- Intra-species competition
- Intra-species cooperation
- Shelter / food storage
- Effort-sparing technologies

5 million years ago



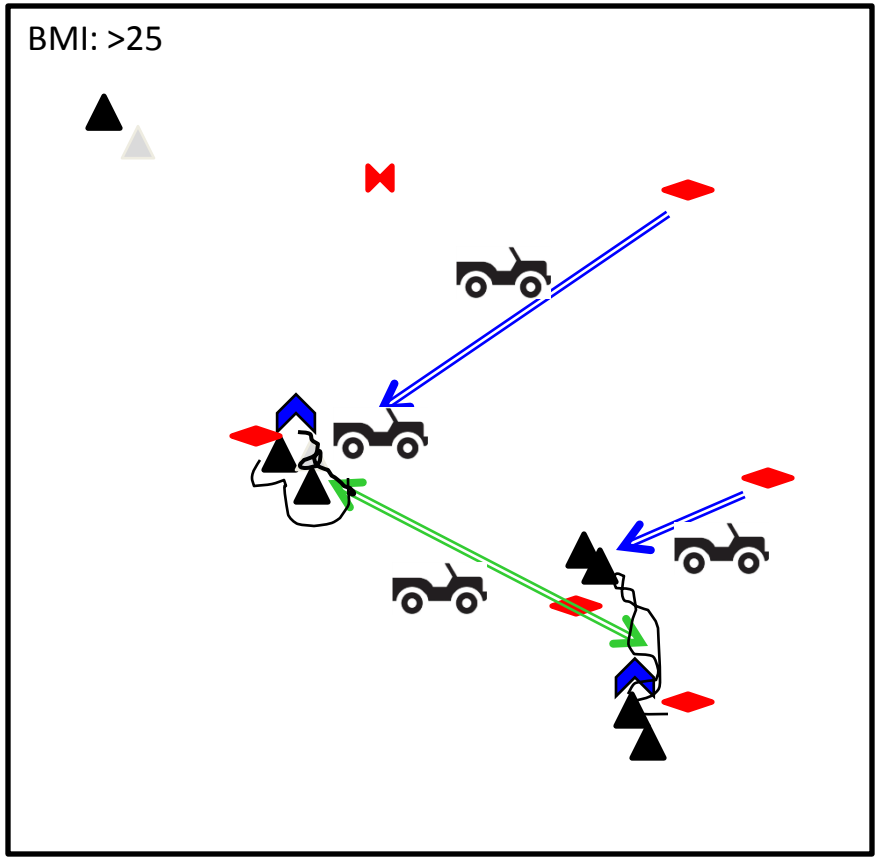
Transition to endurance runner

10,000 years ago



Transition to agriculture

Today



Transition to sedentary / overfed / obese phenotype

Lab Members

Dong Liu
Roy Cutler
Peisu Zhang
Ruiqian Wan
Pamela Yao

Yonquan Luo

Mohamed Mughal
Emmette Hutchison
Kathy Griffioen
Aiwu Cheng

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Elisa Kawamoto
Yue Wang

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Simonetta Camandola

Jeong Yoon
Eitan Okun
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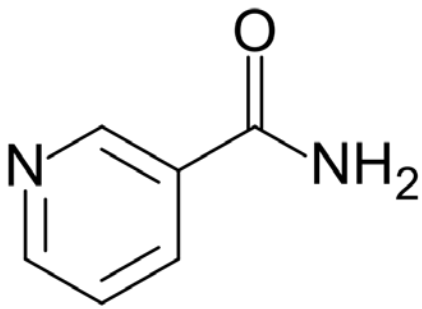
Veerendra Halagappa
Wenzhen Duan
Jaewon Lee
Devin Gary
Ollivier Milhavet
Justin Lathia
Inna Kruman
Alexis Stranahan
Navin Maswood
Sic (Stephen) Chan
Garrie Arumugam
Tae Gen Son
Tim Magnus
Dong-Gyu Jo

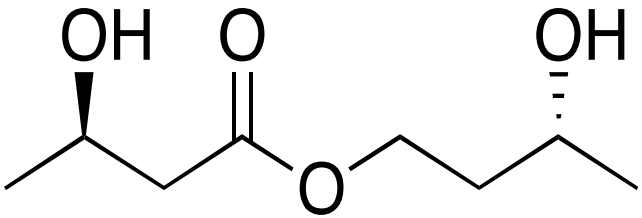
Dietary supplementation with nicotinamide or ketone esters ameliorates behavioral deficits and amyloid pathology in a mouse model of Alzheimer's disease (3xTgAD mice).

Green KN, Steffan JS, Martinez-Coria H, Sun X, Schreiber SS, Thompson LM, LaFerla FM (2008) **Nicotinamide restores cognition in Alzheimer's disease transgenic mice via a mechanism involving sirtuin inhibition and selective reduction of Thr231-phosphotau. J Neurosci.** 28: 11500-10.

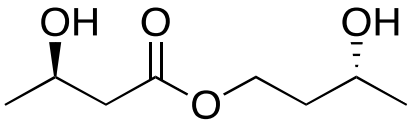
Liu, D., M. Pitta, H. Jiang, J.-H. Lee, G. Zhang, X. Chen, E. M. Kawamoto and M. P. Mattson (2012) **Nicotinamide forestalls pathology and cognitive decline in Alzheimer mice: evidence for improved neuronal bioenergetics and autophagy procession.** *Neurobiol. Aging* 34: 1564-80.



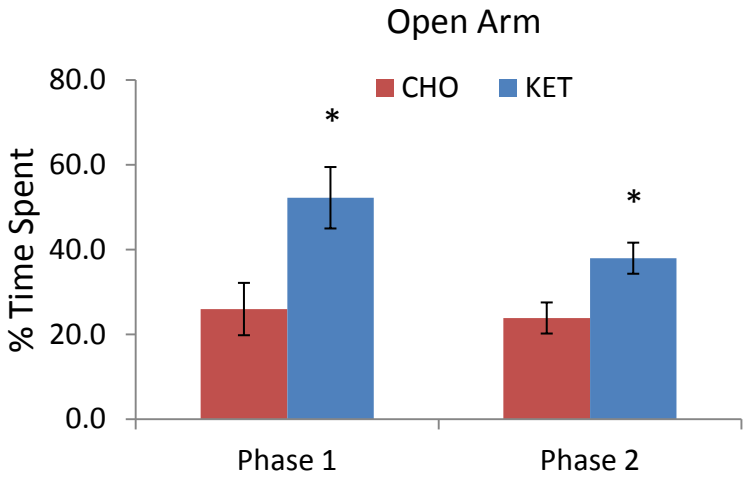
Kashiwaya, Y., C. Bergman, J. H. Lee, R. Wan, M. T. King, M. R. Mughal, E. Okun, K. Clarke, M. P. Mattson and R. L. Veech (2012) **A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease.** *Neurobiol. Aging* 34: 1530-9.

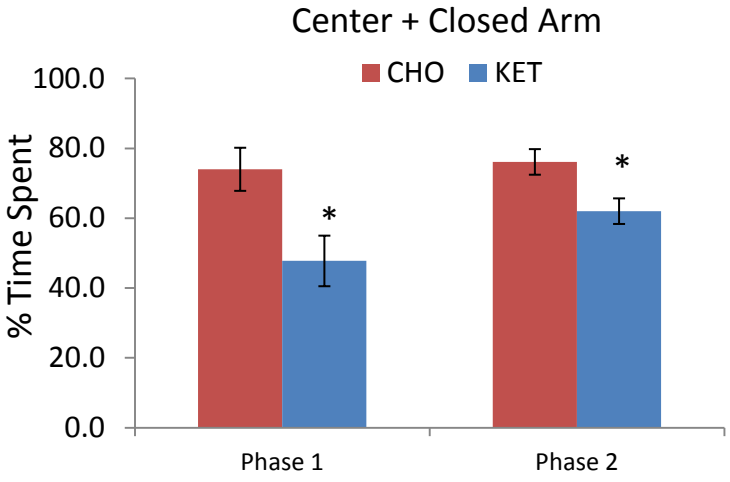


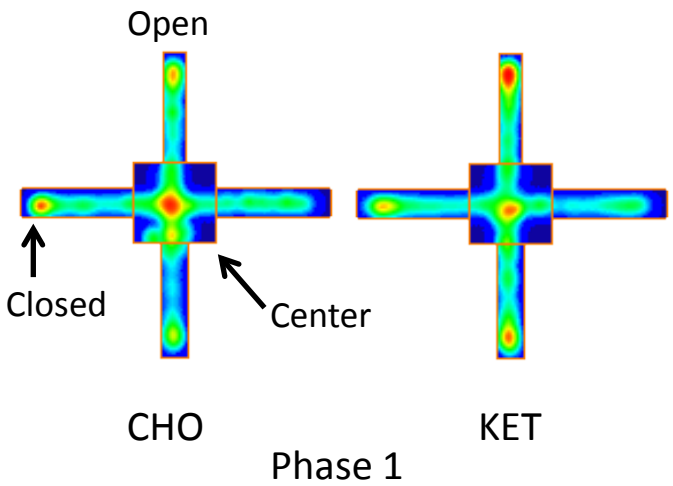
Dietary Supplementation with Ketone Esters (D-β-hydroxybutyrate and (R)-1,3- butanediol) Ameliorates Anxiety-Like Behavior in 3xTgAD Mice

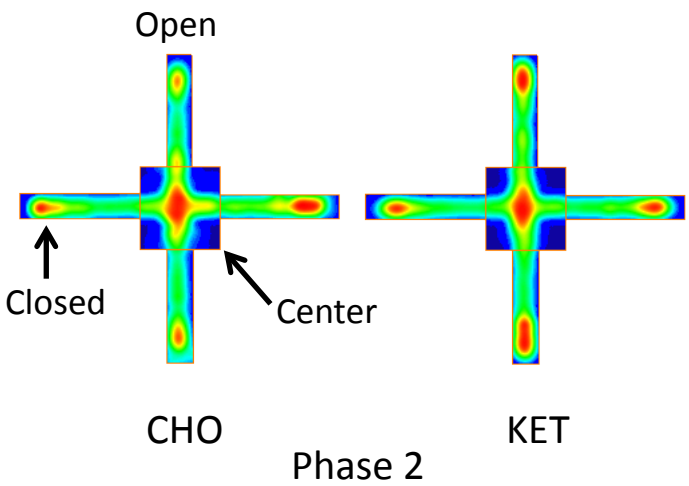


Elevated Plus Maze



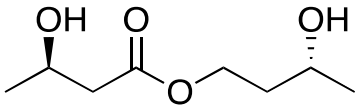




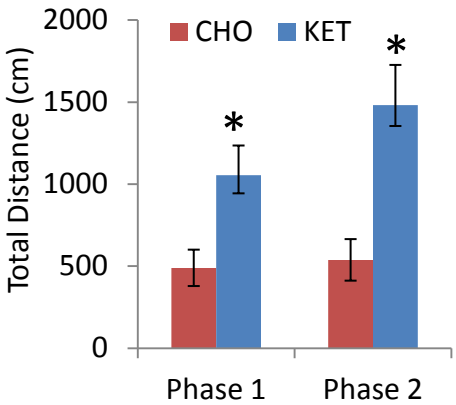


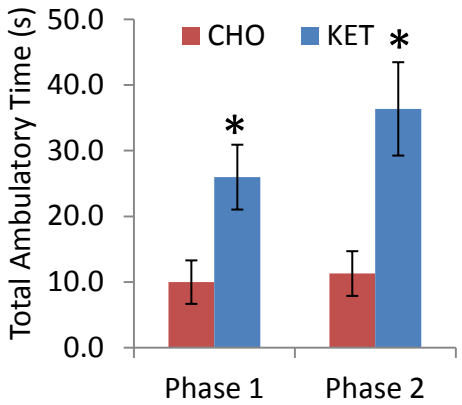
Kashiwaya et al., 2012

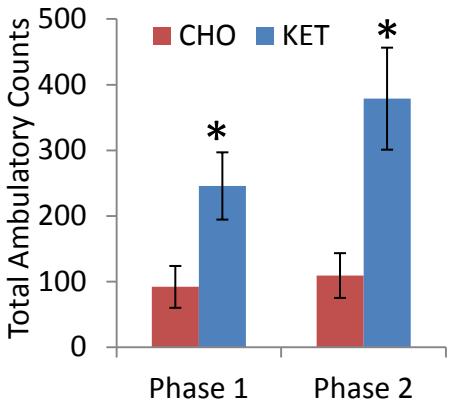
Dietary Supplementation with Ketone Esters (D-β-hydroxybutyrate and (R)-1,3-butanediol) Ameliorates Anxiety-Like Behavior in 3xTgAD Mice

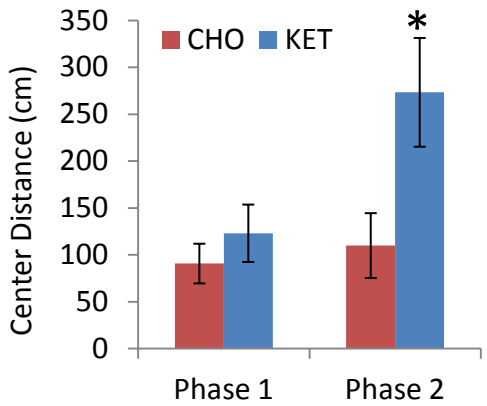


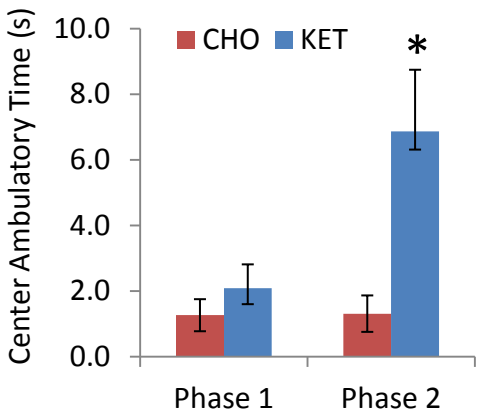
Open Field

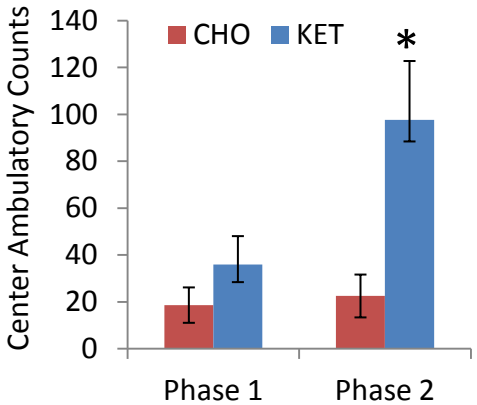




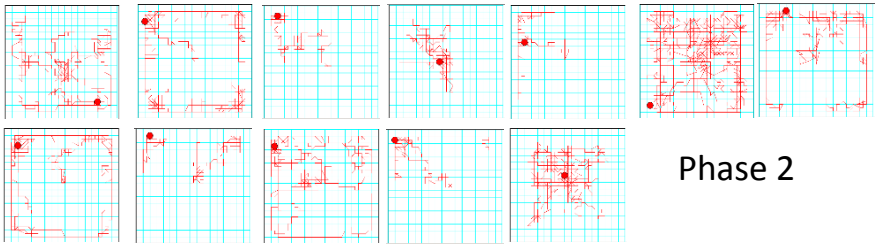






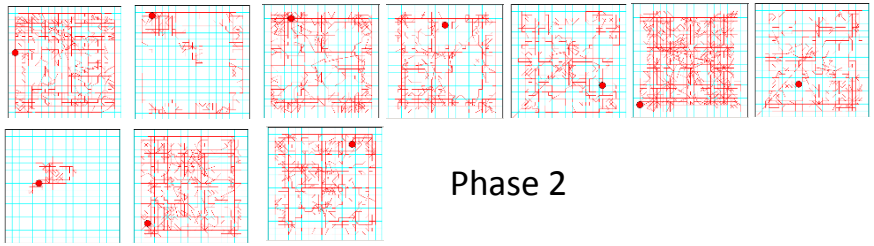


CHO



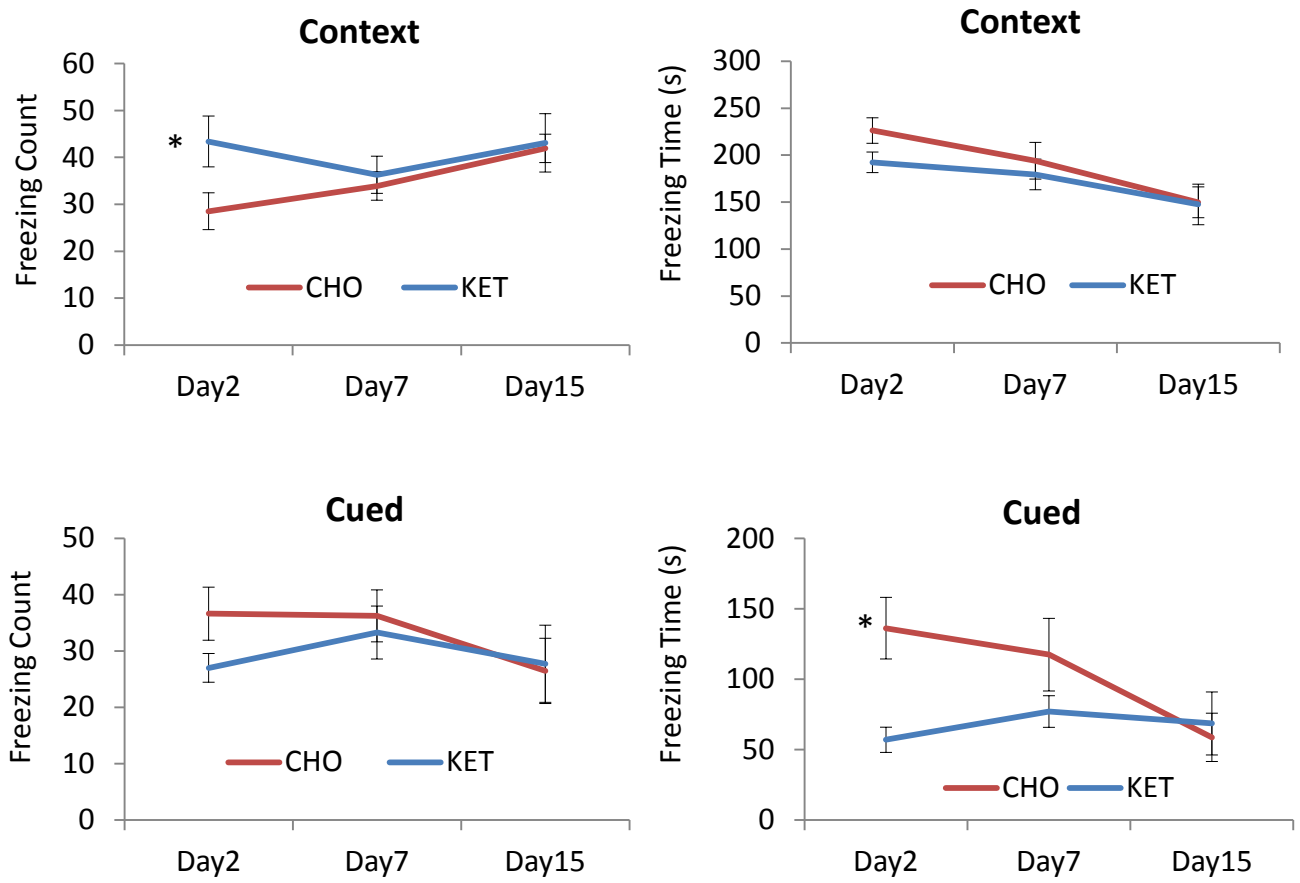
Phase 2

KET



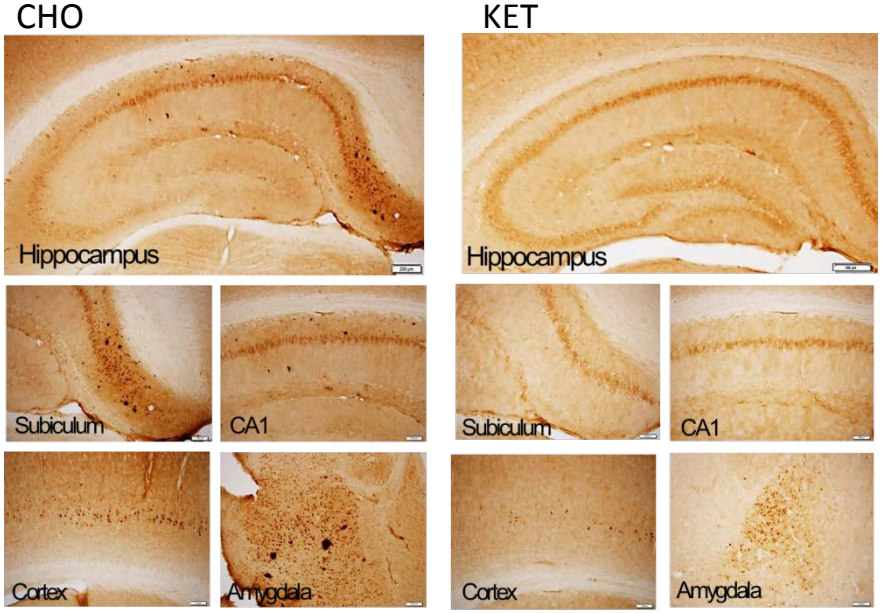
Phase 2

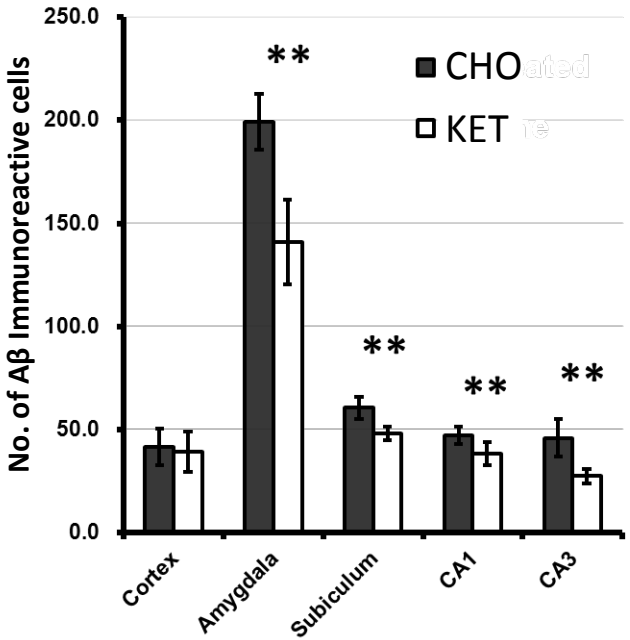
Ketone ester-fed 3xTgAD mice exhibit stronger context-dependent fear response related to hippocampal memory and a more rapid extinction of amygdala-dependent tone-related conditioned fear compared to 3xTgAD mice fed the control diet.



Aβ Immunoreactivity

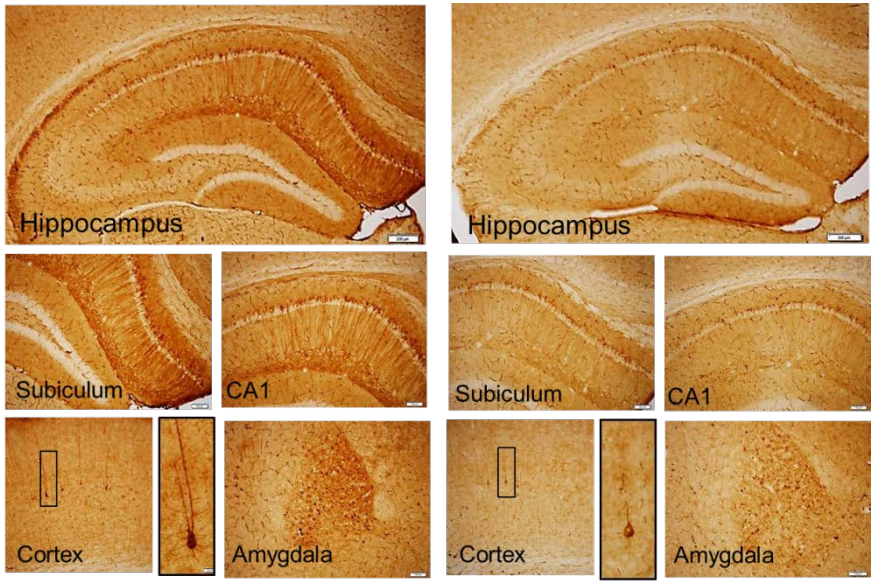
A

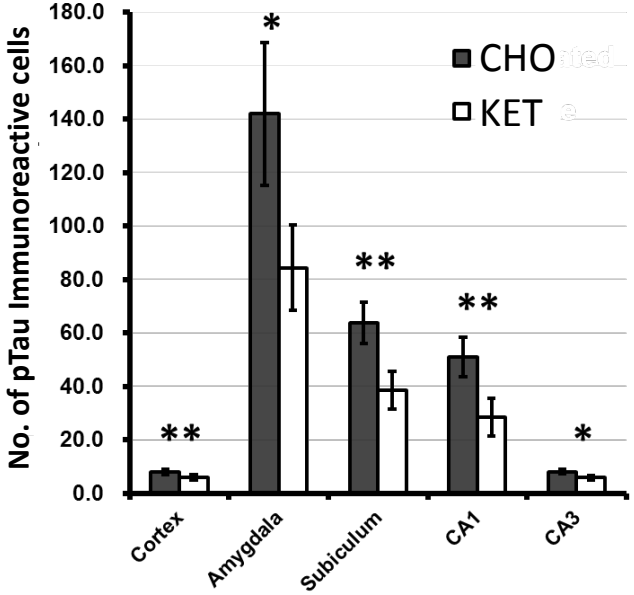




pTau Immunoreactivity

B

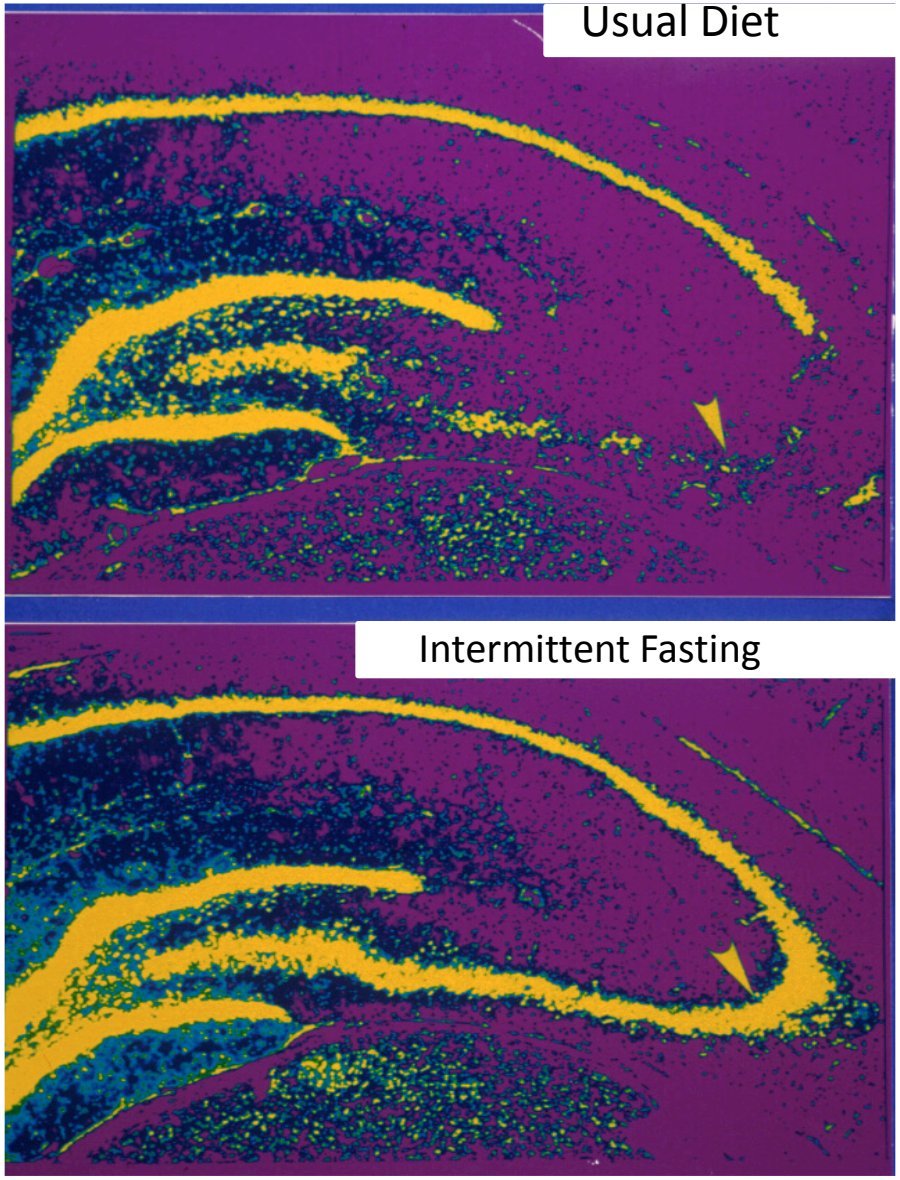


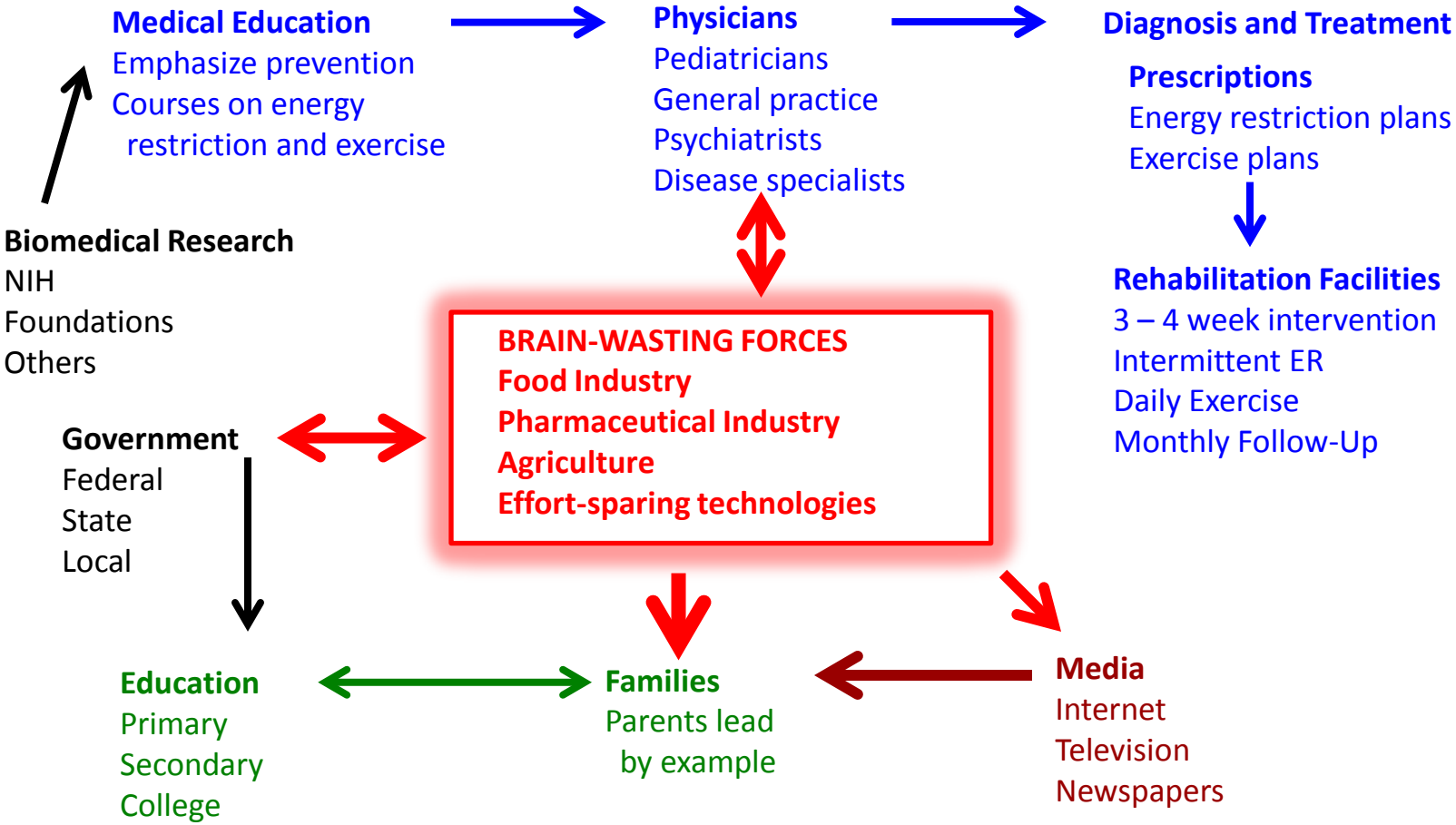


DISPELLING THE DEMONS (epileptic seizures)

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.





Mattson MP. Energy Intake and Exercise as Determinants of Brain Health and Vulnerability to Injury and Disease. *Cell Metabolism* 2012; 16: 706-722.

The Fasting Cure

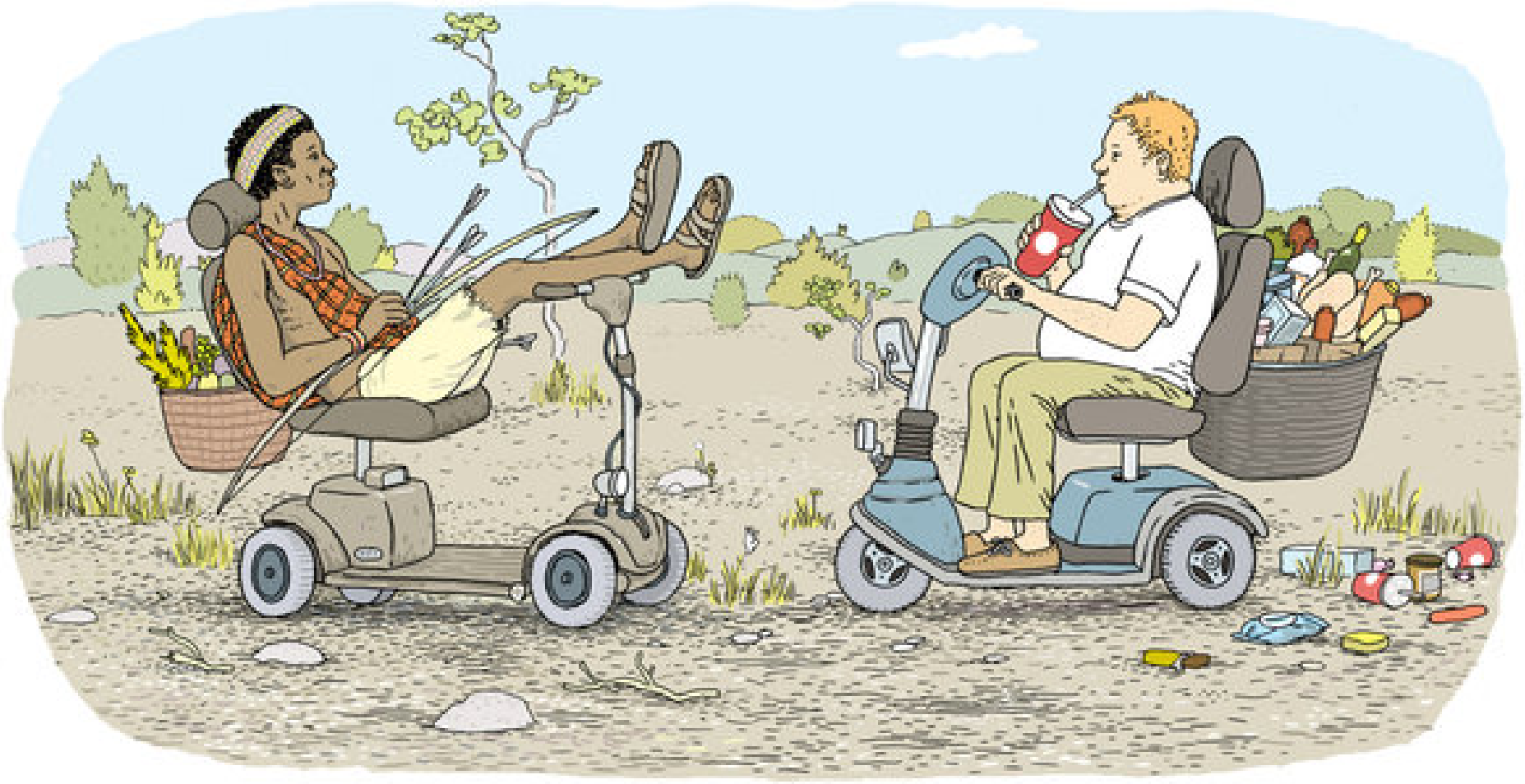
by

UPTON SINCLAIR

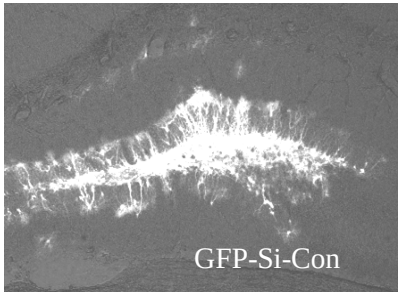
IN the *Cosmopolitan Magazine* for May, 1910, and in the *Contemporary Review* (London) for April, 1910, I published an article dealing with my experiences in fasting. I have written a great many magazine articles, but never one which attracted so much attention as this. The

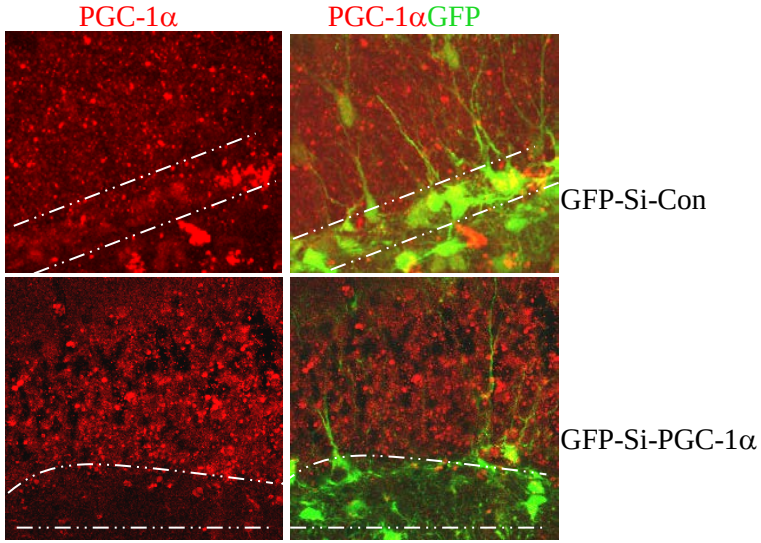
My object in publishing this book is two-fold: first, to have something to which I can refer people, so that I will not have to answer half a dozen "fasting letters" every day for the rest of my life; and second, in the hope of attracting sufficient attention to the subject to interest some scientific men in making a real investigation of it. To-day we know certain facts about what is called "autointoxication"; 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.

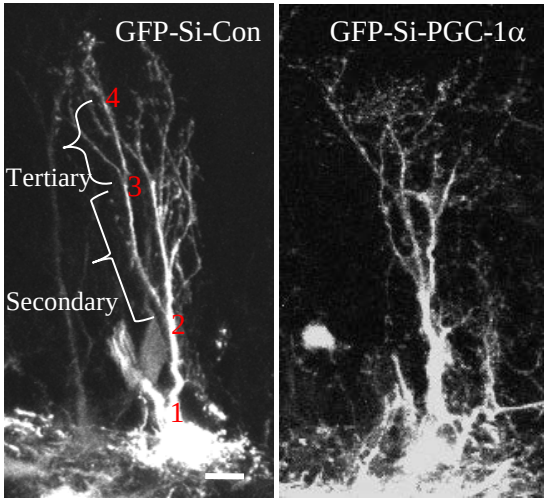
Upton Sinclair

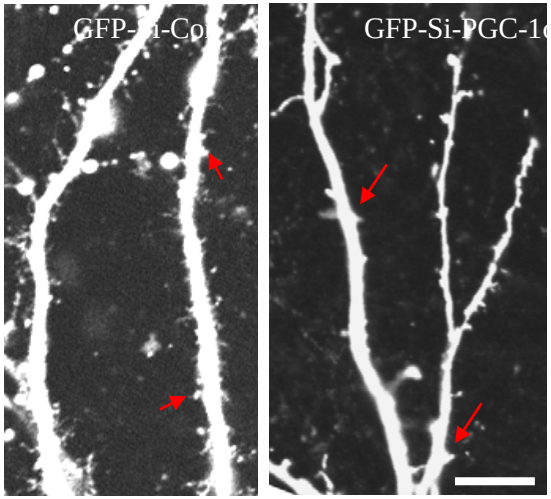


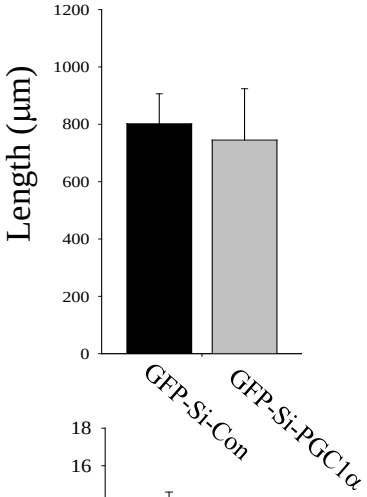
NY Times / Anders Nilsen

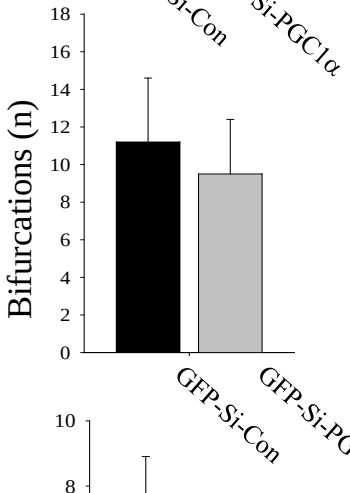

GFP-Si-Con

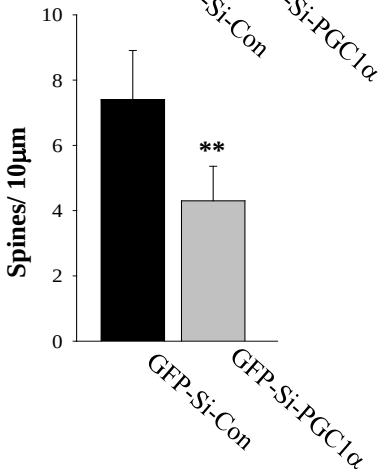

PGC-1α
PGC-1αGFP
GFP-Si-Con
GFP-Si-PGC-1α

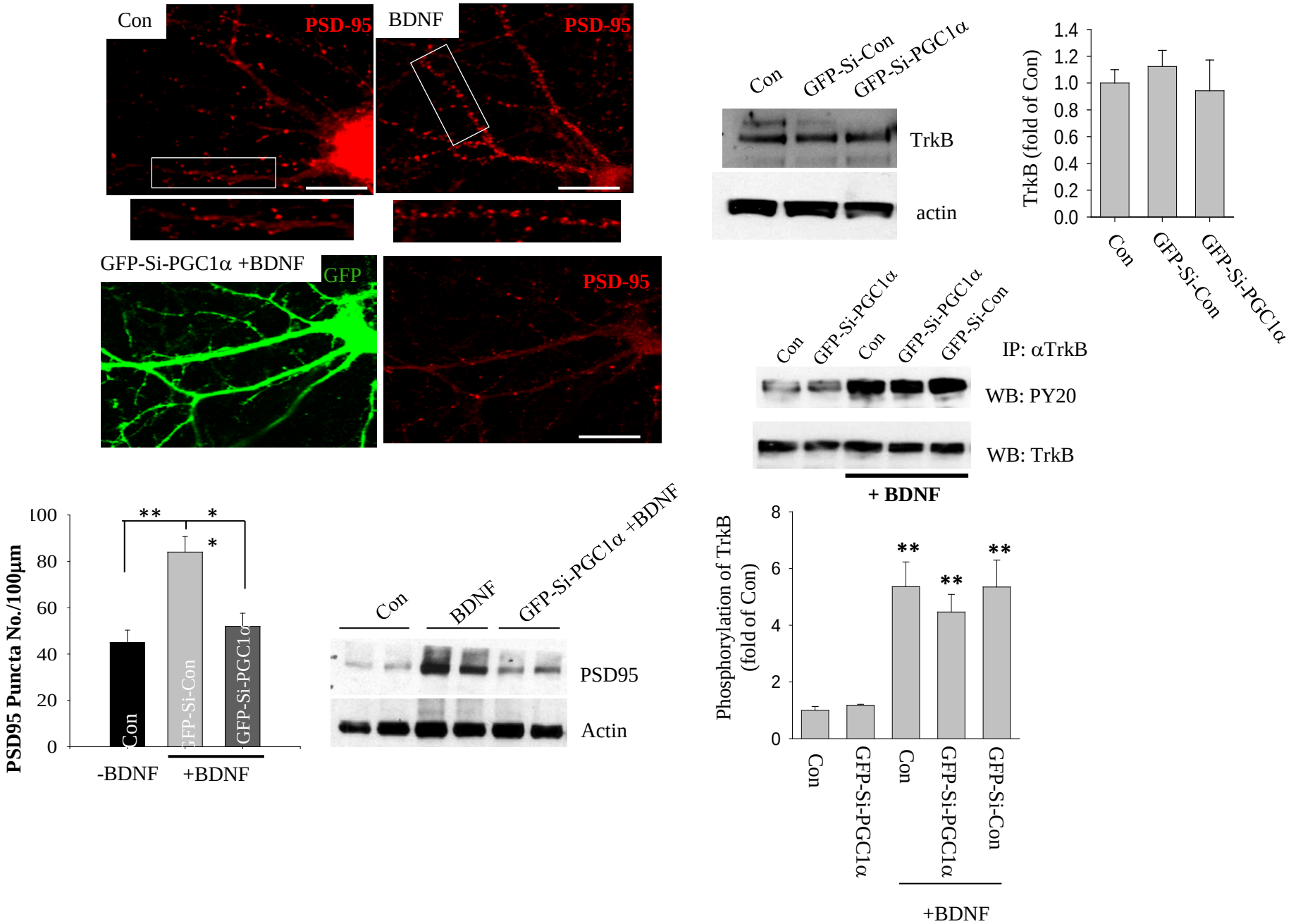

GFP-Si-Con
GFP-Si-PGC-1α
4
Tertiary
3
Secondary
2
1




Length (μm)
1200
1000
800
600
400
200
0
GFP-Si-Con
GFP-Si-PGC1α


Bifurcations (n)
18
16
14
12
10
8
6
4
2
0
GFP-Si-Con
GFP-Si-PGC1α


Spines/ 10μm
10
8
6
4
2
0
**
GFP-Si-Con
GFP-Si-PGC1α


Con
PSD-95
BDNF
PSD-95
GFP-Si-PGC1α +BDNF
GFP
PSD-95
Con
GFP-Si-Con
GFP-Si-PGC1α
TrkB
actin
TrkB (fold of Con)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Con
GFP-Si-Con
GFP-Si-PGC1α
Con
GFP-Si-PGC1α
Con
GFP-Si-PGC1α
GFP-Si-Con
IP: αTrkB
WB: PY20
WB: TrkB
+ BDNF
PSD95 Puncta No./100μm
100
80
60
40
20
0
**
*
*
Con
GFP-Si-Con
GFP-Si-PGC1α
-BDNF
+BDNF
Con
BDNF
GFP-Si-PGC1α +BDNF
PSD95
Actin
Phosphorylation of TrkB (fold of Con)
8
6
4
2
0
**
**
**
Con
GFP-Si-PGC1α
Con
GFP-Si-PGC1α
GFP-Si-Con
+BDNF