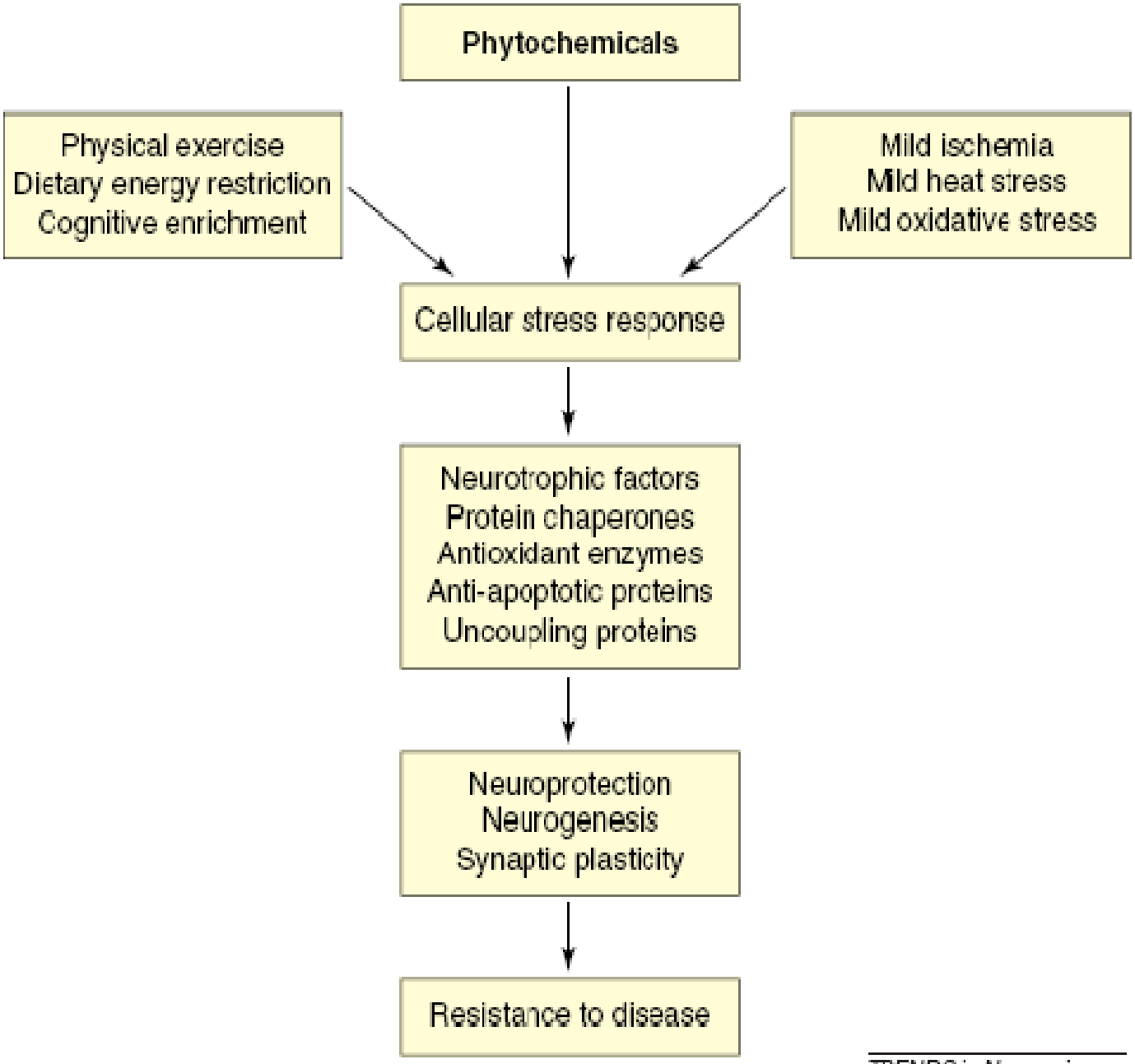
Biological stress response terminology: Integrating the concepts of adaptive response and preconditioning stress within a hormetic dose-response framework. **Toxicol Appl Pharmacol. 2007 Mar 7; [Epub ahead of print]**

Calabrese EJ, Bachmann KA, Bailer AJ, Bolger PM, Borak J, Cai L, Cedergreen N, Cherian MG, Chiueh CC, Clarkson TW, Cook RR, Diamond DM, Doolittle DJ, Dorato MA, Duke SO, Feinendegen L, Gardner DE, Hart RW, Hastings KL, Hayes AW, Hoffmann GR, Ives JA, Jaworowski Z, Johnson TE, Jonas WB, Kaminski NE, Keller JG, Klaunig JE, Knudsen TB, Kozumbo WJ, Lettieri T, Liu SZ, Maisseu A, Maynard KI, Masoro EJ, McClellan RO, Mehendale HM, Mothersill C, Newlin DB, Nigg HN, Oehme FW, Phalen RF, Philbert MA, Rattan SI, Riviere JE, Rodricks J, Sapolsky RM, Scott BR, Seymour C, Sinclair DA, Smith-Sonneborn J, Snow ET, Spear L, Stevenson DE, Thomas Y, Tubiana M, Williams GM, Mattson MP.

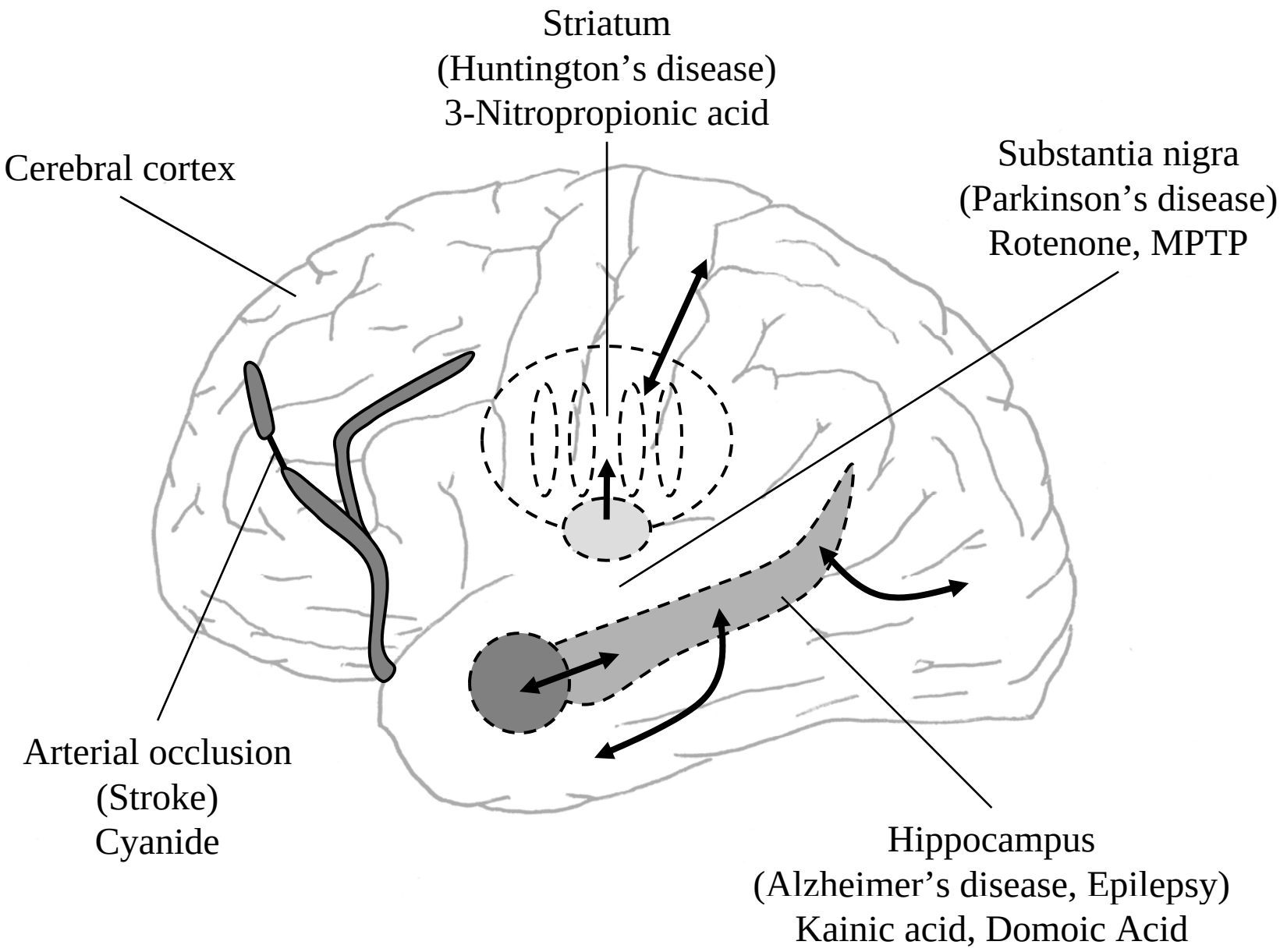
Hormesis refers to a process in which exposure to a low dose of a chemical agent or environmental factor that is damaging at higher doses induces a beneficial effect on the cell or organism. In biomedical sciences the terms “pre-conditioning” or “adaptive stress response” are often used instead of hormesis.

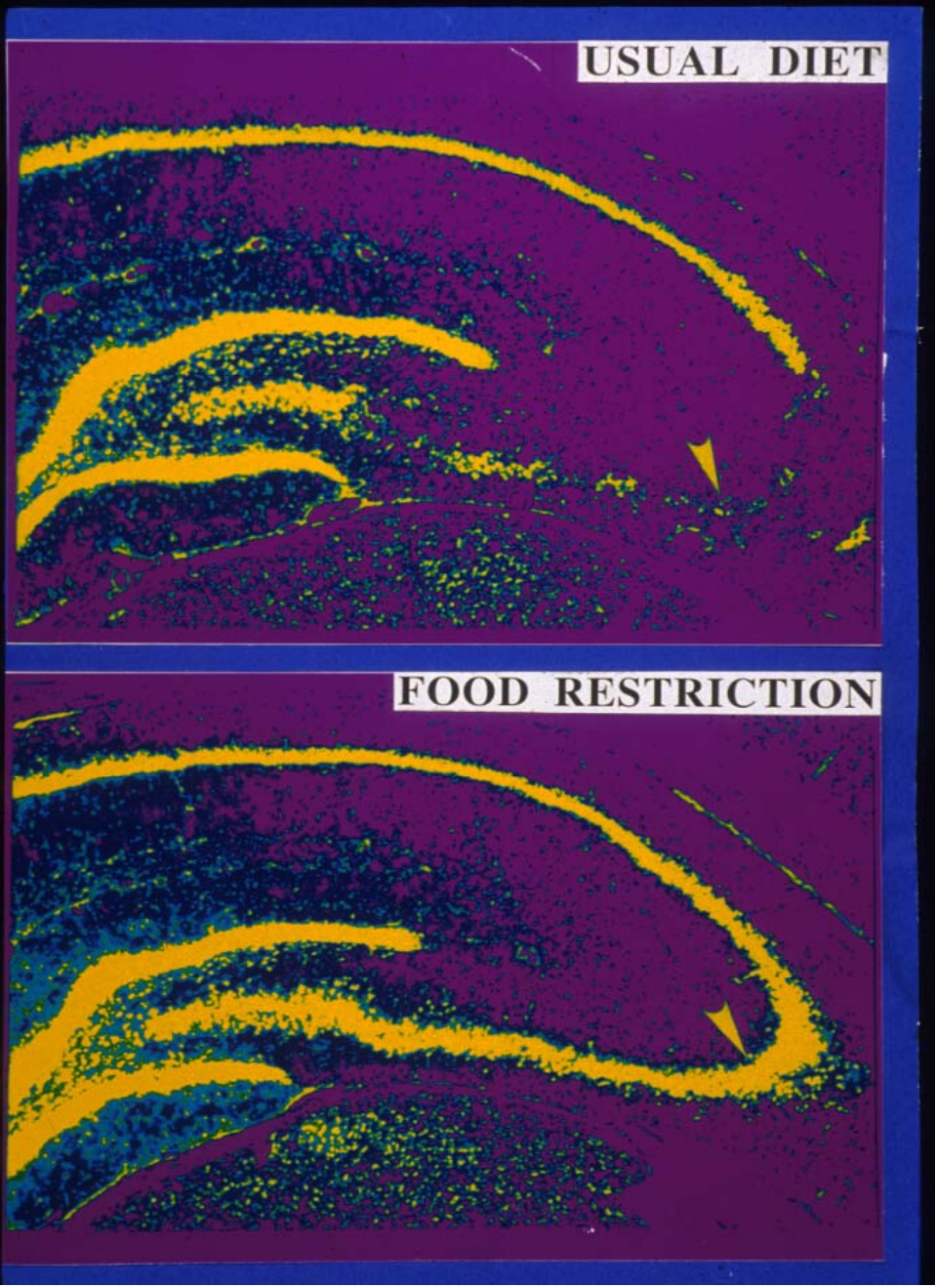
The term hormesis has been widely used in the toxicology field where it is defined as an adaptive response characterized by biphasic dose responses of generally similar quantitative features with respect to amplitude and range of the stimulatory response that are either directly induced or the result of compensatory biological processes following an initial disruption in homeostasis.

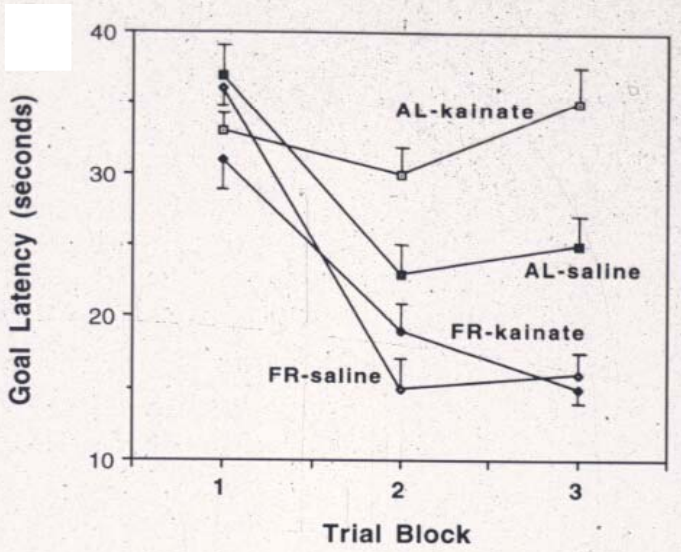
At the cellular and molecular levels hormesis involves activation of adaptive stress response pathways that result in increased expression of cytoprotective proteins (e.g., heat-shock proteins, antioxidant enzymes and anti-apoptotic proteins.

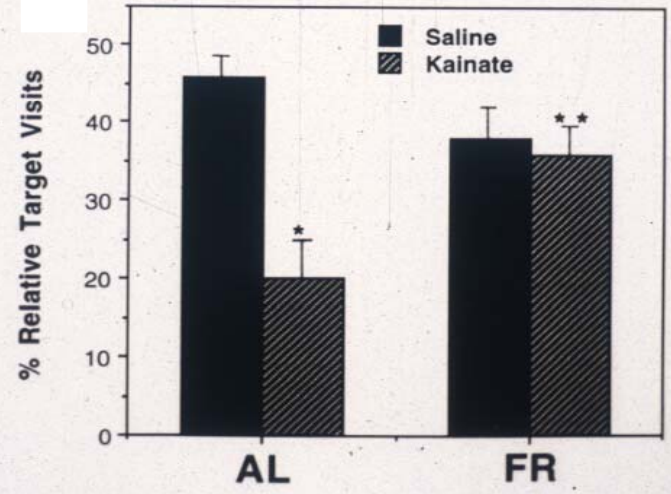


TRENDS in Neurosciences

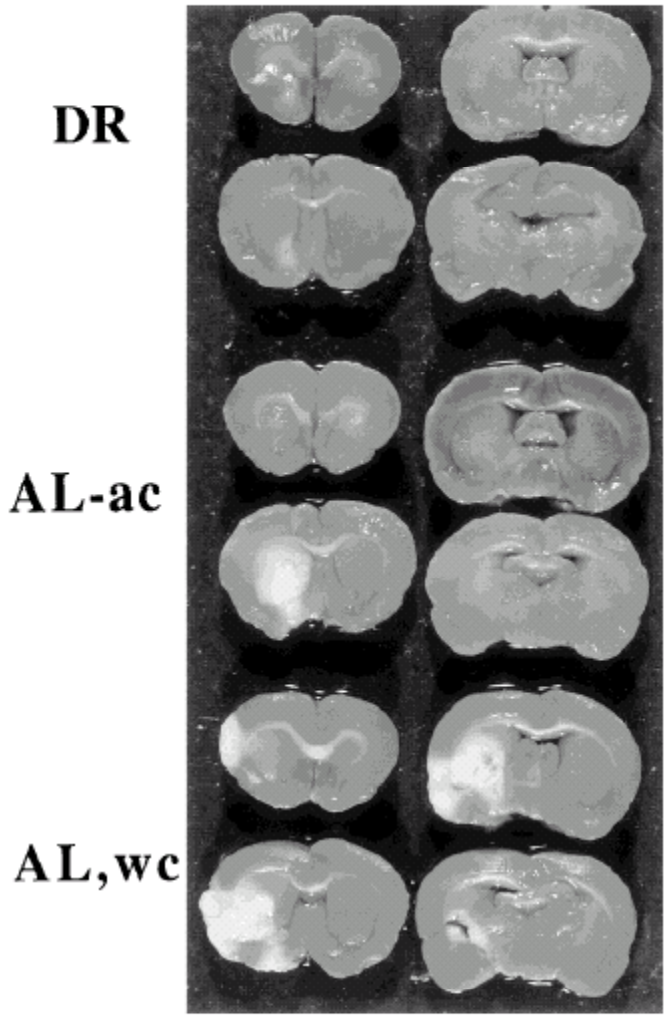

Striatum
(Huntington's disease)
3-Nitropropionic acid
Cerebral cortex
Substantia nigra
(Parkinson's disease)
Rotenone, MPTP
Arterial occlusion
(Stroke)
Cyanide
Hippocampus
(Alzheimer's disease, Epilepsy)
Kainic acid, Domoic Acid

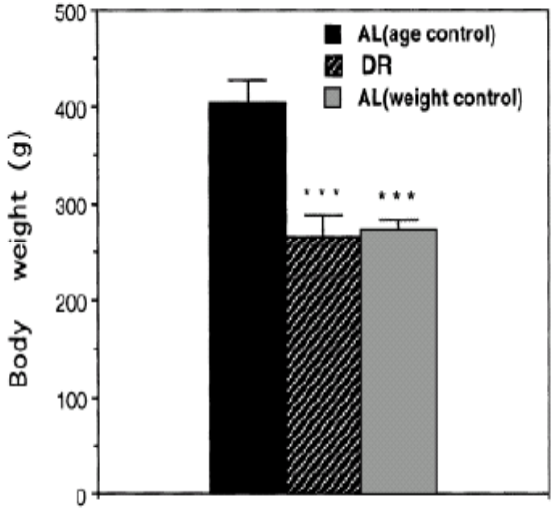


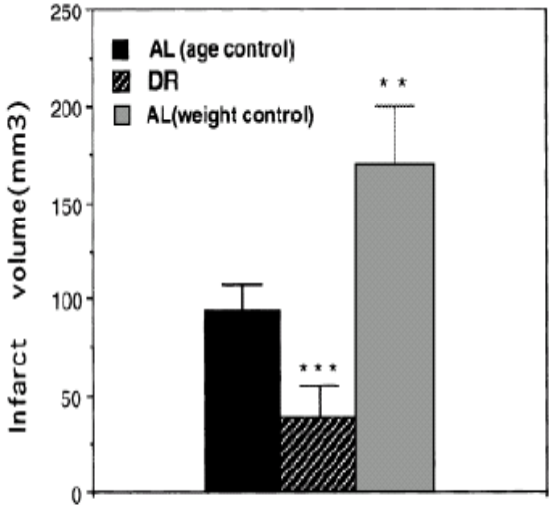


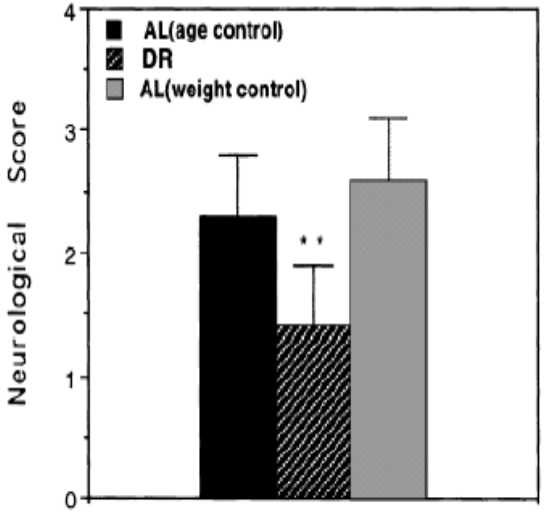


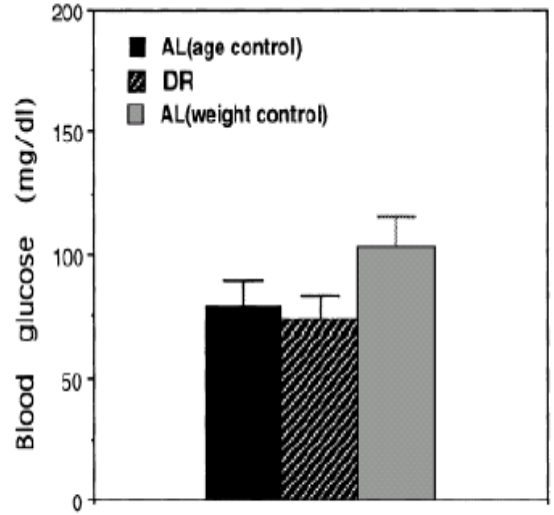
Bruce-Keller et al. (1999) Ann. Neurol. 45: 8-15


DR
AL-ac
AL,wc


Body weight (g)
500
400
300
200
100
0
AL(age control)
DR
AL(weight control)
***
***

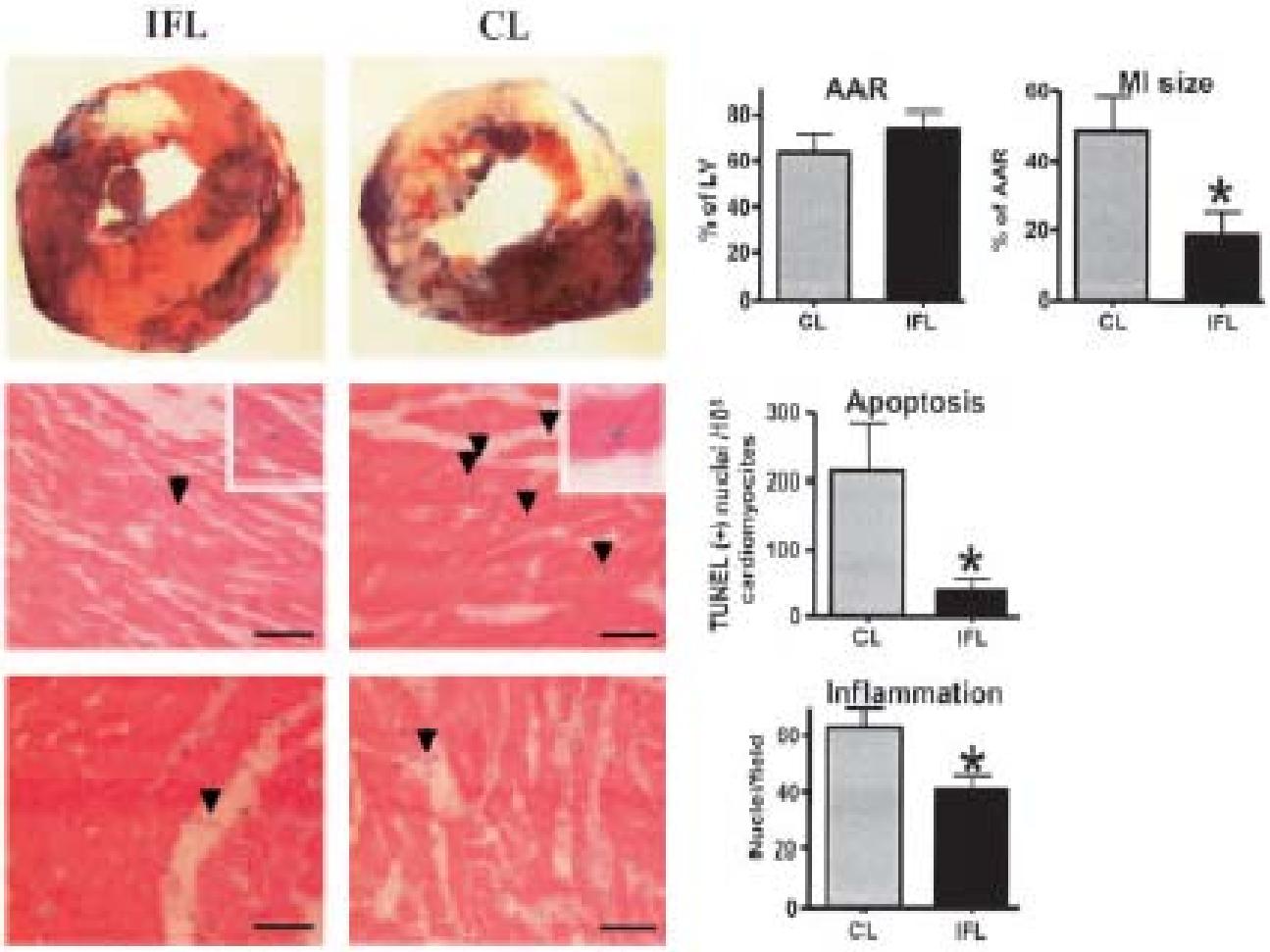

Infarct volume(mm3)
250
200
150
100
50
0
AL (age control)
DR
AL(weight control)
**
***

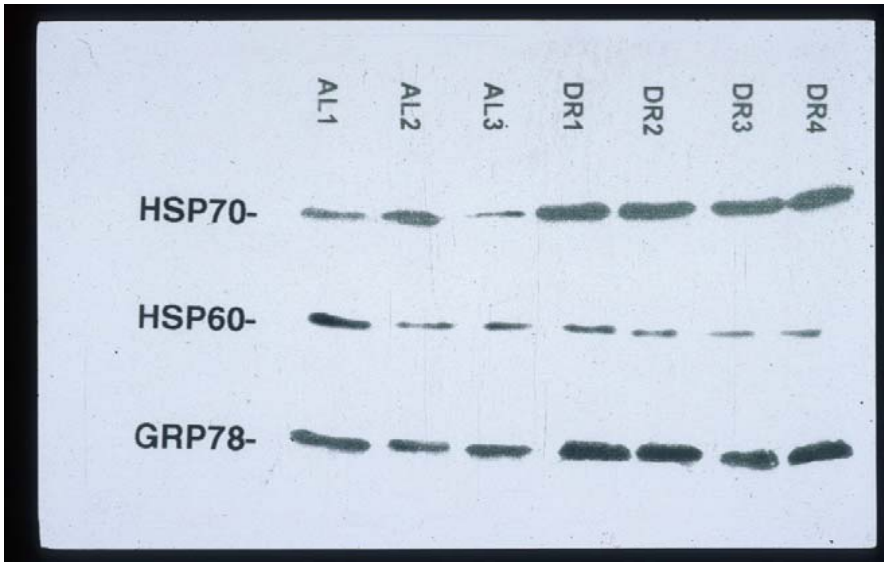

Neurological Score
4
3
2
1
0
AL(age control)
DR
AL(weight control)
**

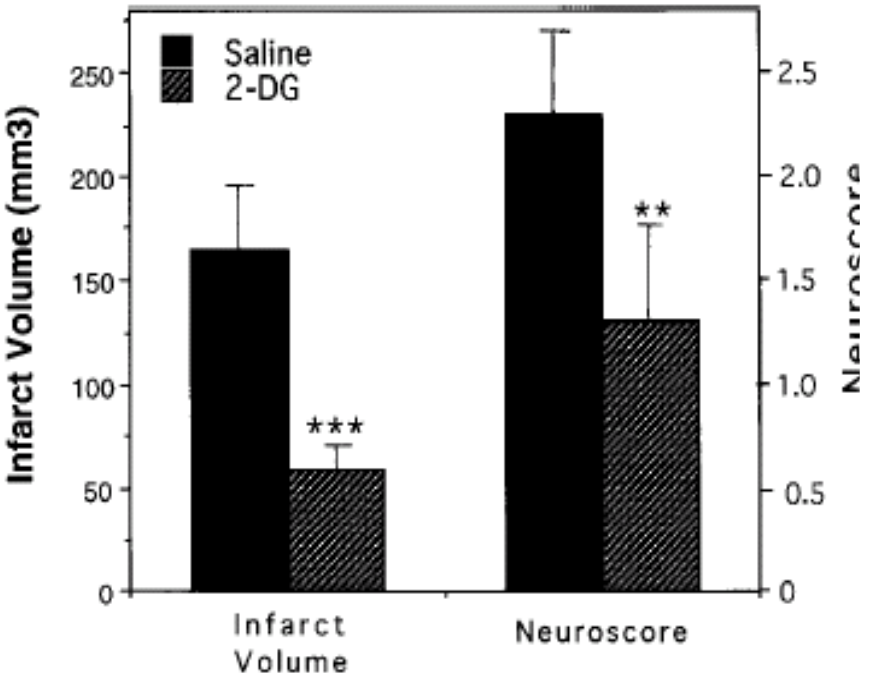

Blood glucose (mg/dl)
200
150
100
50
0
AL(age control)
DR
AL(weight control)

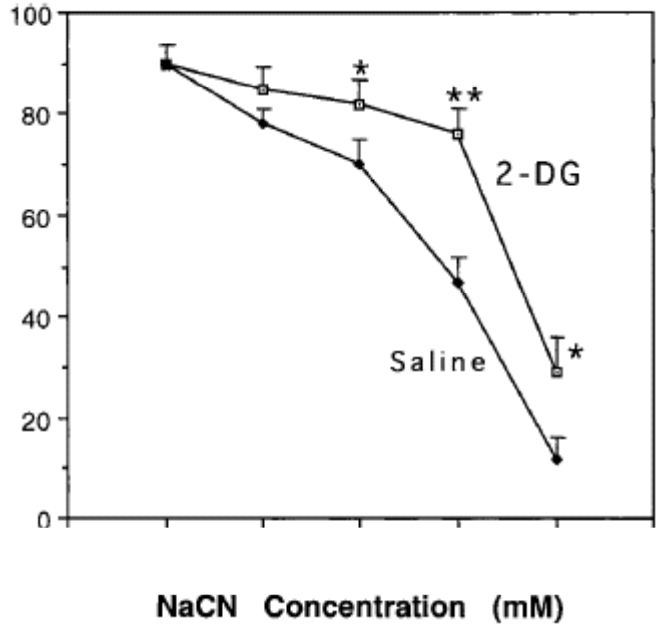
Cardioprotection by Intermittent Fasting in Rats

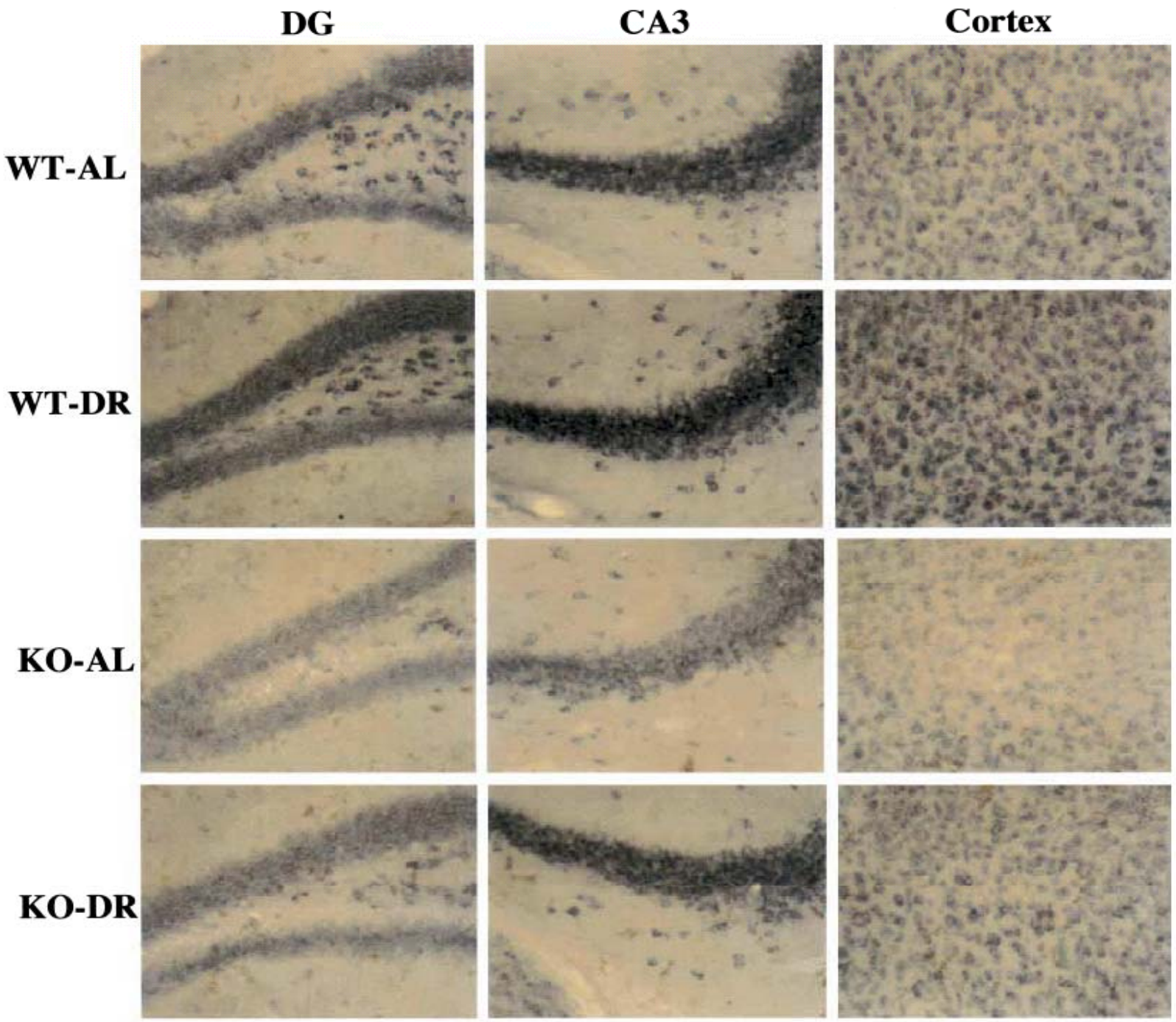
Ismayil Ahmet, MD, PhD*; Ruiqian Wan, PhD*; Mark P. Mattson, PhD;
Edward G. Lakatta, MD; Mark Talan, MD, PhD




AL1
AL2
AL3
DR1
DR2
DR3
DR4
HSP70-
HSP60-
GRP78-

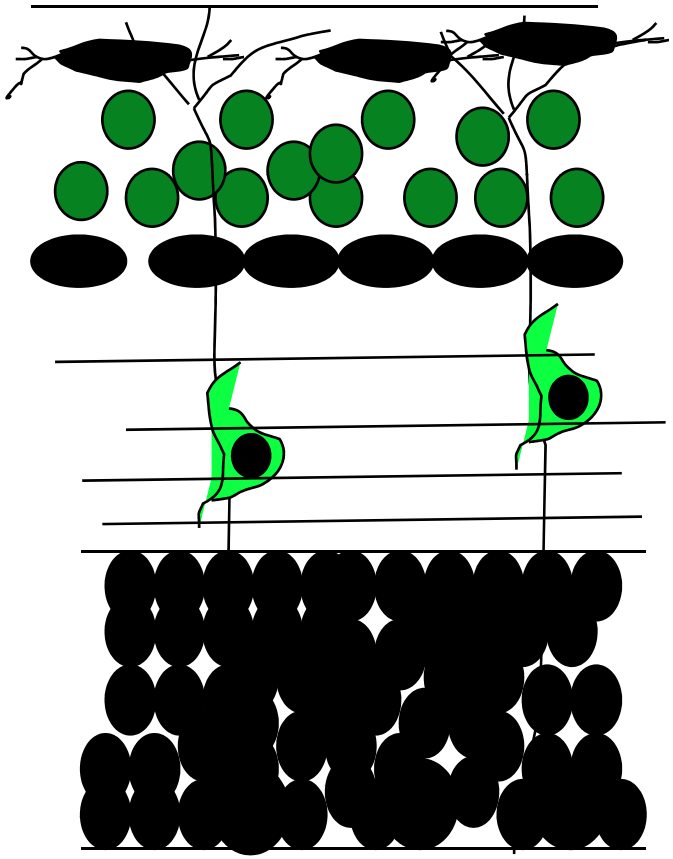

Saline
2-DG
Infarct Volume (mm3)
250
200
150
100
50
0
2.5
2.0
1.5
1.0
0.5
0
***
**
Infarct Volume
Neuroscore

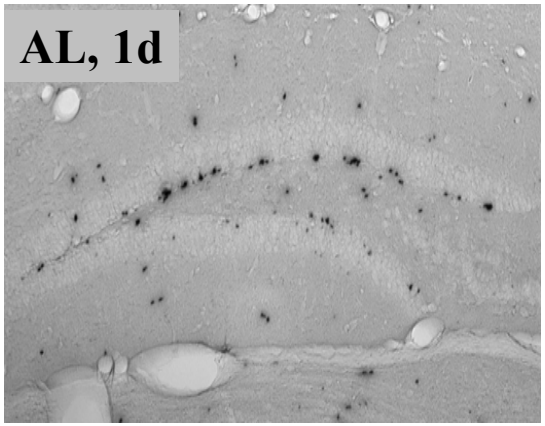

100
80
60
40
20
0
*
**
2-DG
Saline
*
NaCN Concentration (mM)

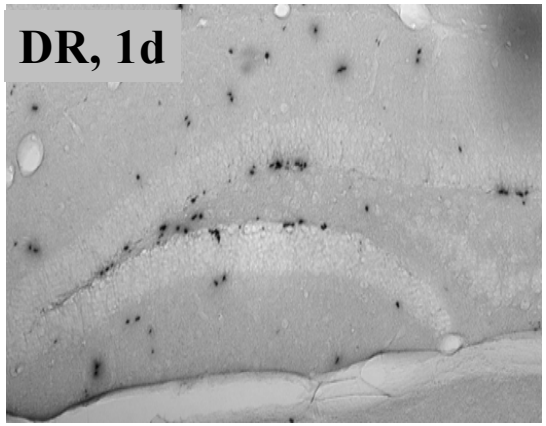

DG
CA3
Cortex
WT-AL
WT-DR
KO-AL
KO-DR

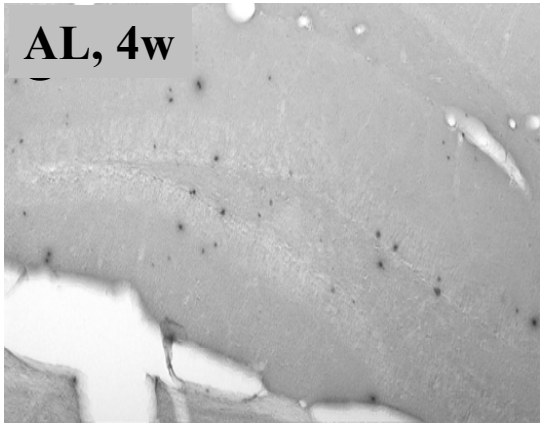
Cheng, A., S. Wang, M. S. Rao and M. P. Mattson (2002) Nitric oxide acts in a positive feedback loop with BDNF to regulate neural progenitor cell proliferation and differentiation in the mammalian brain. *Dev. Biol.* 258: 319-333..

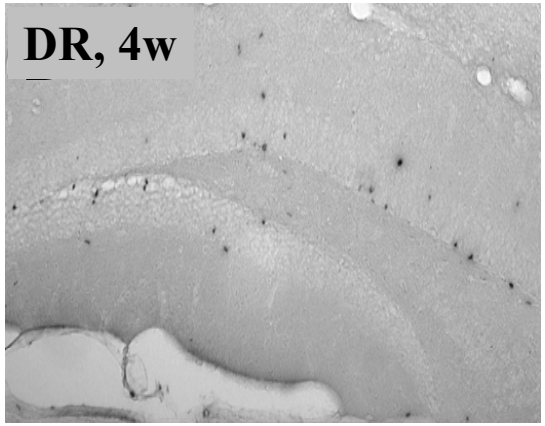
Lee, J., K. Seroogy and M. P. Mattson (2002) Dietary restriction enhances neurotrophin expression and neurogenesis in the hippocampus of adult mice. *J. Neurochem.* 80: 539-547.









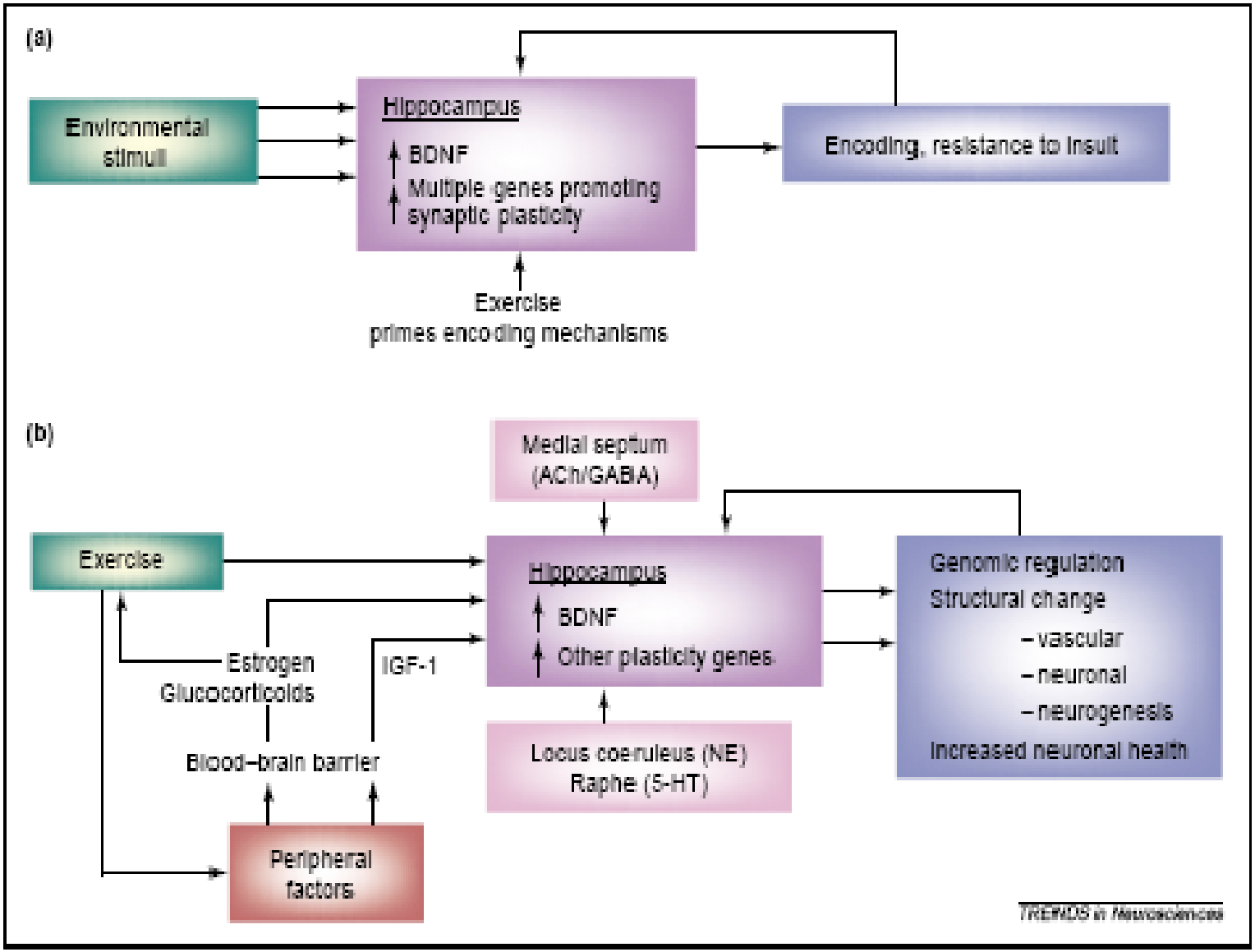


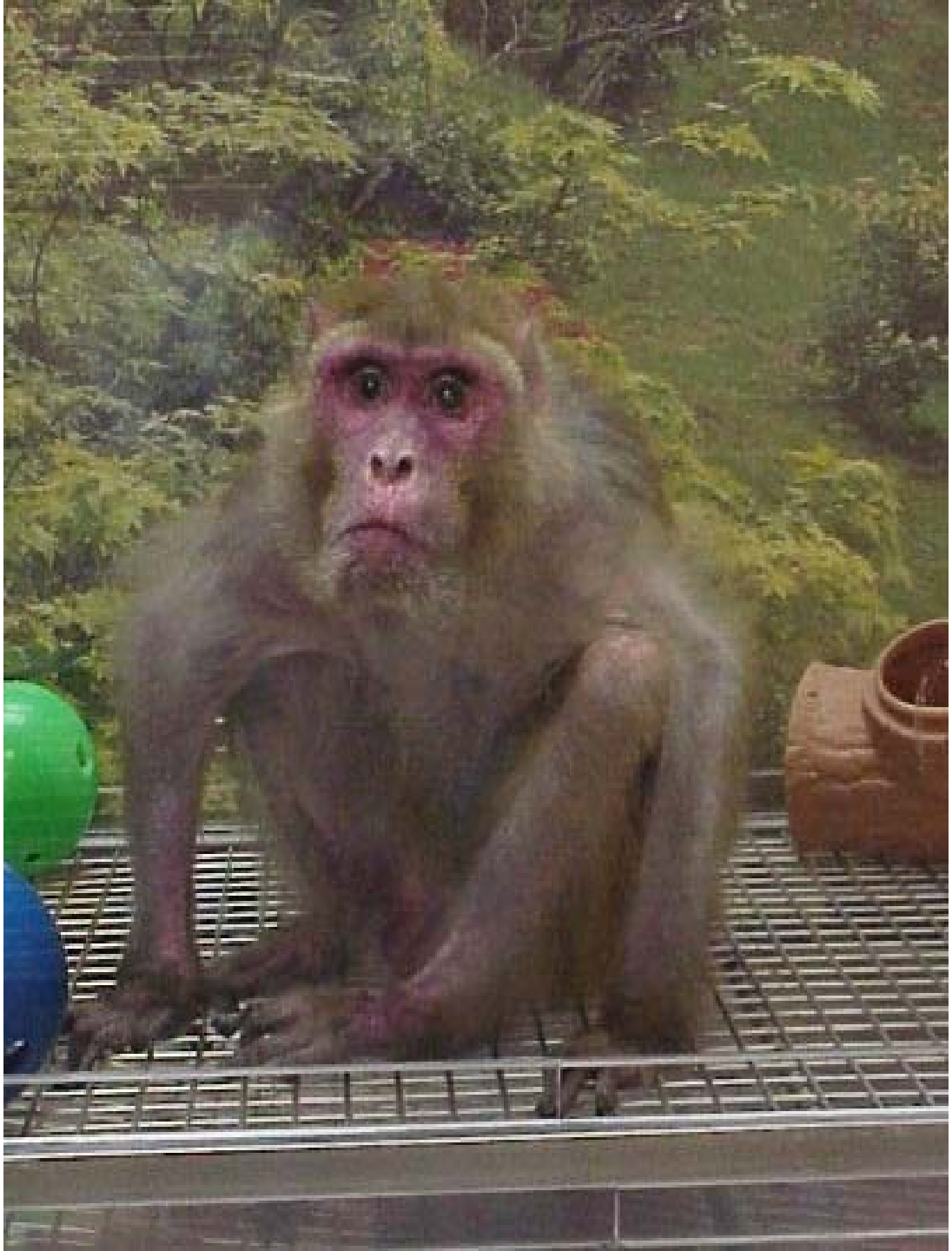
Proliferation and survival of BrdU-labeled cells in the dentate gyrus of mice fed AL in comparison with mice maintained on DR.

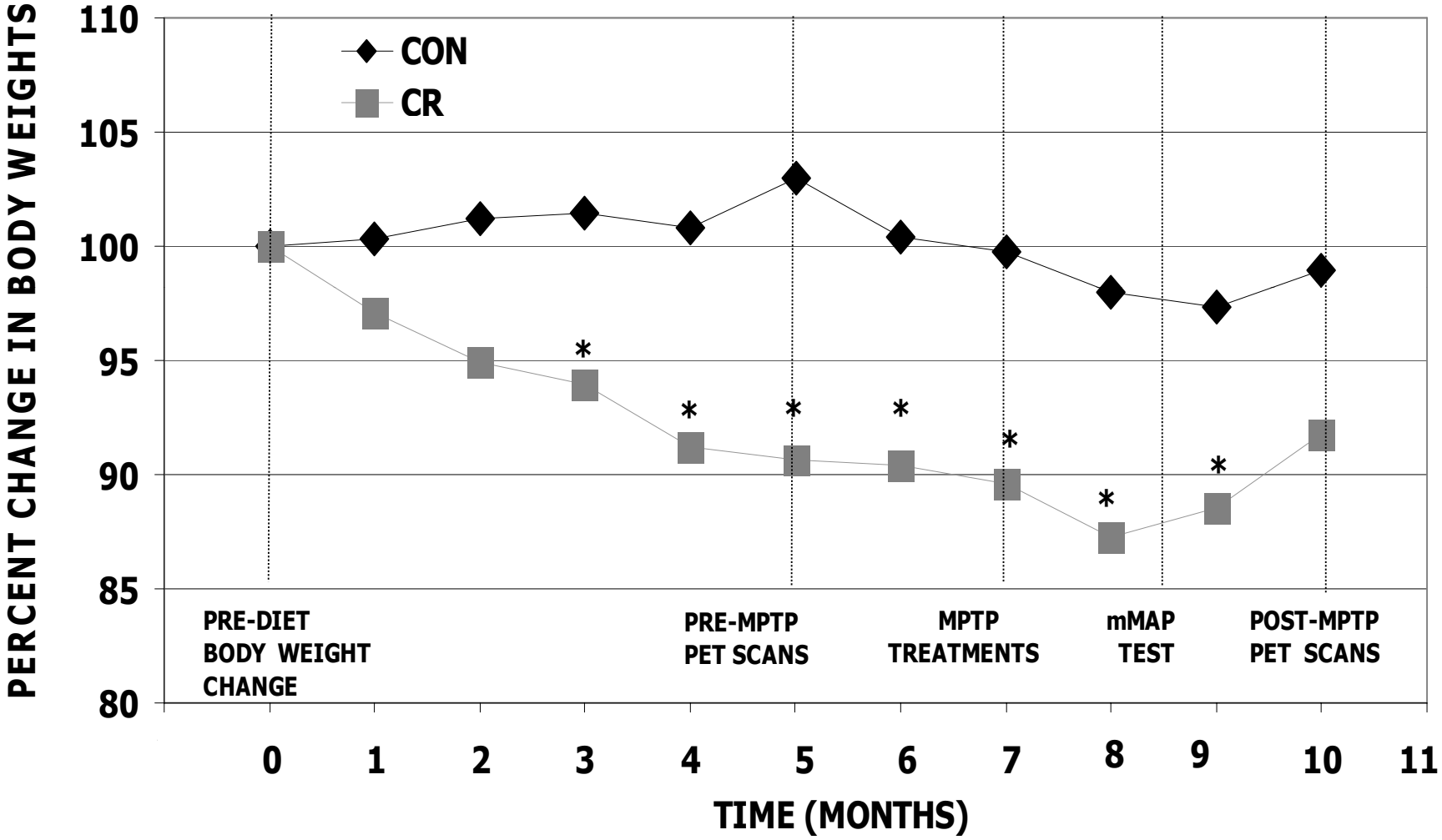
	Wild-Type Mice		BDNF+/- Mice	
	AL	DR	AL	DR
Proliferation, 1 day	3533 ± 177.6	3226 ± 105.8	2789 ± 189.2[a]	3146 ± 264.6
Survival, 4 wks	967 ± 84.7	1496 ± 80.9[d]	626 ± 48.0[a,b]	1028 ± 88.8[c]
Survival (%), 4 wks	**27 ± 2.4**	**46 ± 2.5[d]**	**22 ± 1.7[b]**	**33 ± 2.8[c]**
Regional Volume*, 1 day	0.174 ± 0.013	0.175 ± 0.010	0.148 ± 0.005	0.162 ± 0.010
Regional Volume*, 4 wks	0.201 ± 0.011	0.190 ± 0.011	0.147 ± 0.008[a,b]	0.175 ± 0.016

*mm^3

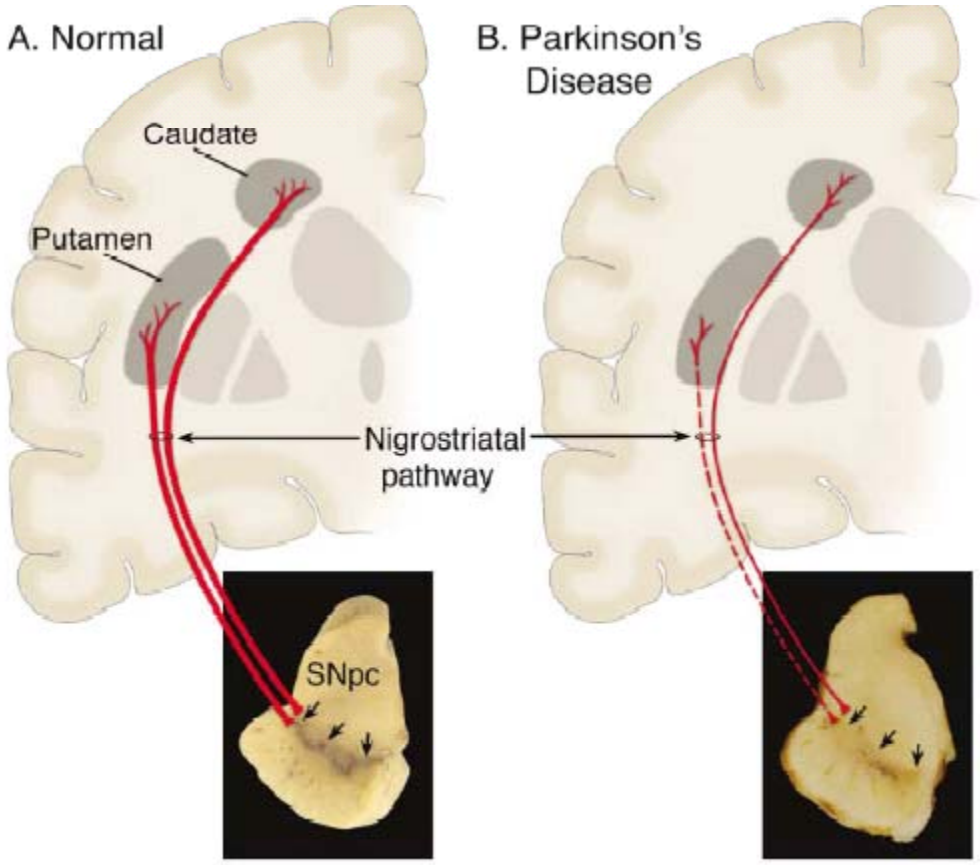
All mice received BrdU (100 mg per kg; 5 injections during a 2 day time period). Cell proliferation was assessed on 1 day after last injection. Survival of BrdU-labeled cells in the dentate gyrus were determined 4 weeks after last injection (n = 4 to 7 per group). All data are presented as means ± standard error. [a]P<0.02 compared to the wild-type AL value, [b]P<0.02 compared to the wild-type DR value, [c]P<0.02 compared to the BDNF +/- AL value, [d]P<0.01 compared to each of the other values.

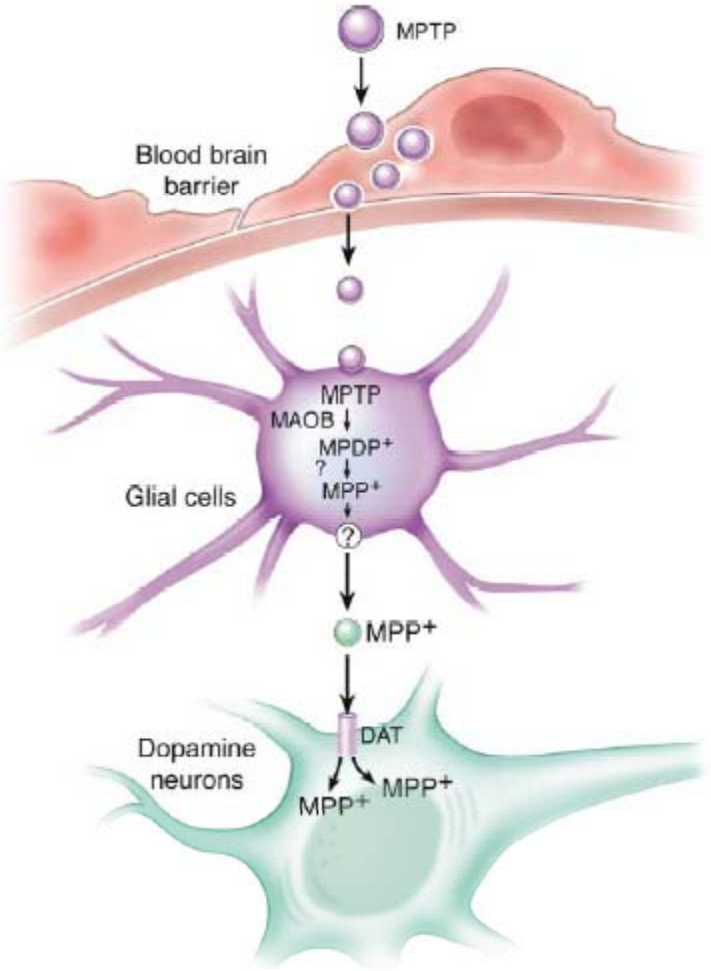

(a)
Environmental stimuli
Hippocampus
BDNF
Multiple genes promoting synaptic plasticity
Encoding, resistance to insult
Exercise primes encoding mechanisms
(b)
Medial septum (ACh/GABA)
Exercise
Hippocampus
BDNF
Other plasticity genes
Genomic regulation
Structural change
– vascular
– neuronal
– neurogenesis
Increased neuronal health
Estrogen
Glucocorticoids
IGF-1
Blood–brain barrier
Locus coeruleus (NE)
Raphe (5-HT)
Peripheral factors
TRENDS in Neurosciences



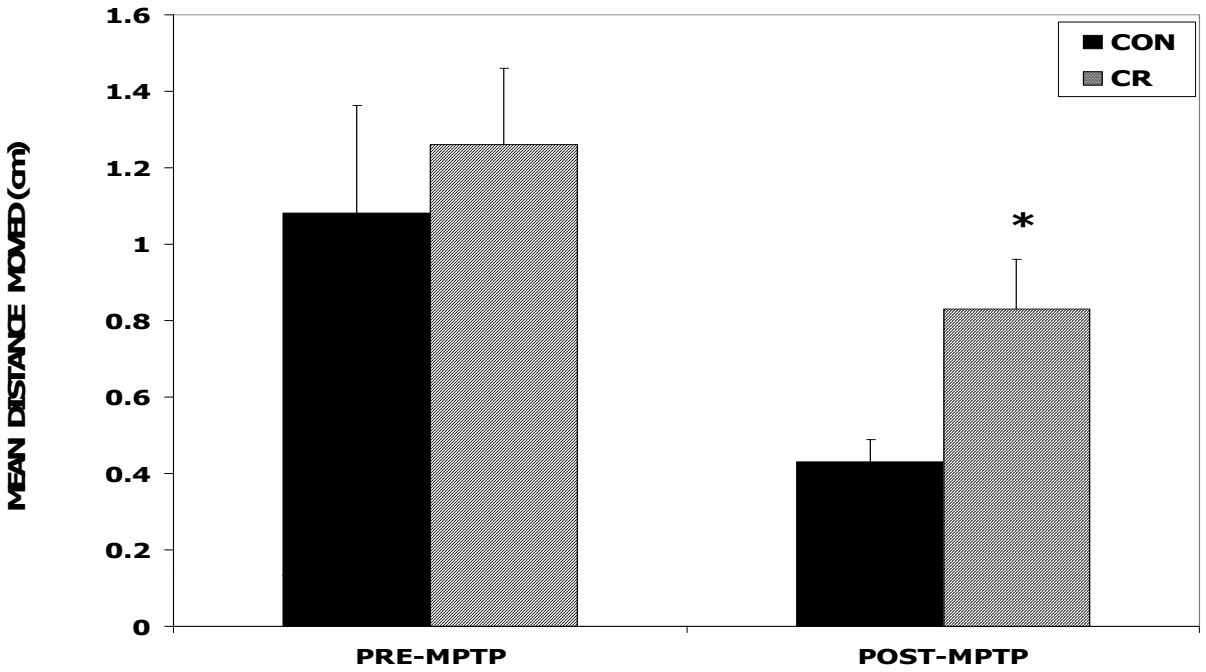


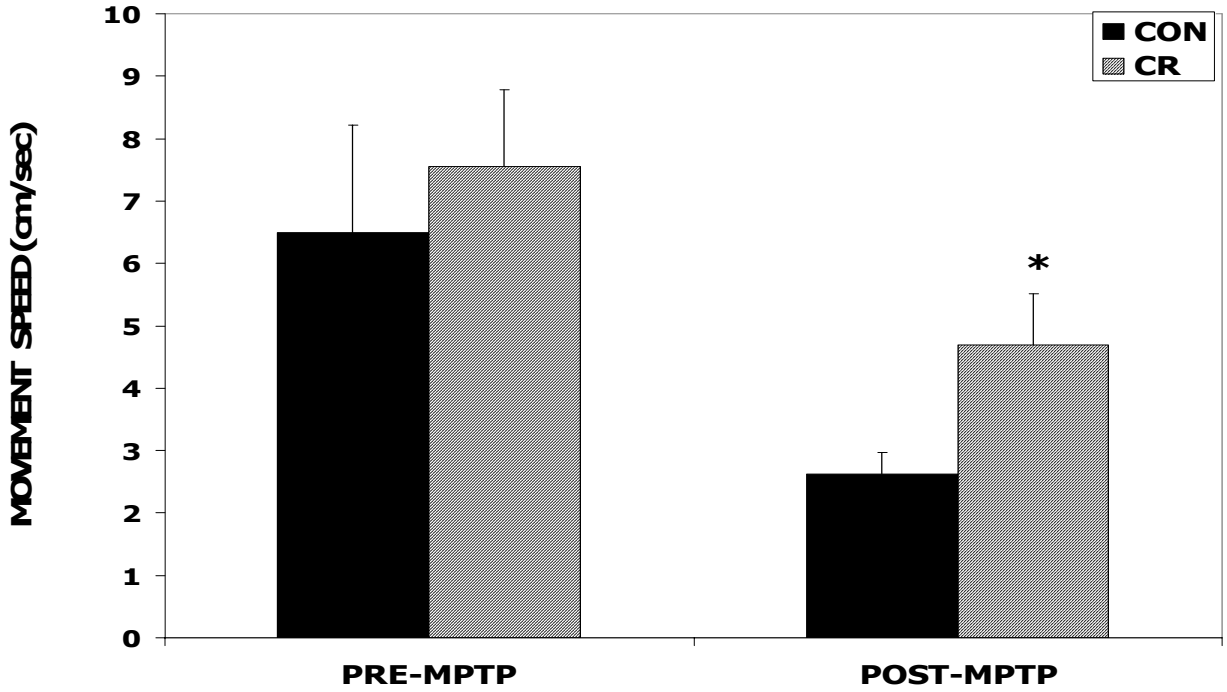
Maswood et al. (2004) PNAS 101:18171-18176

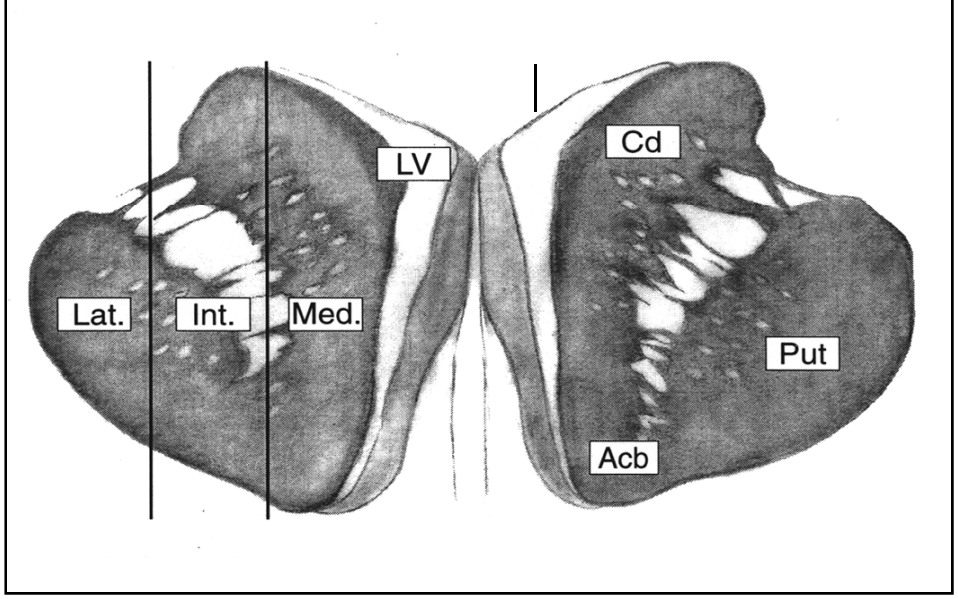


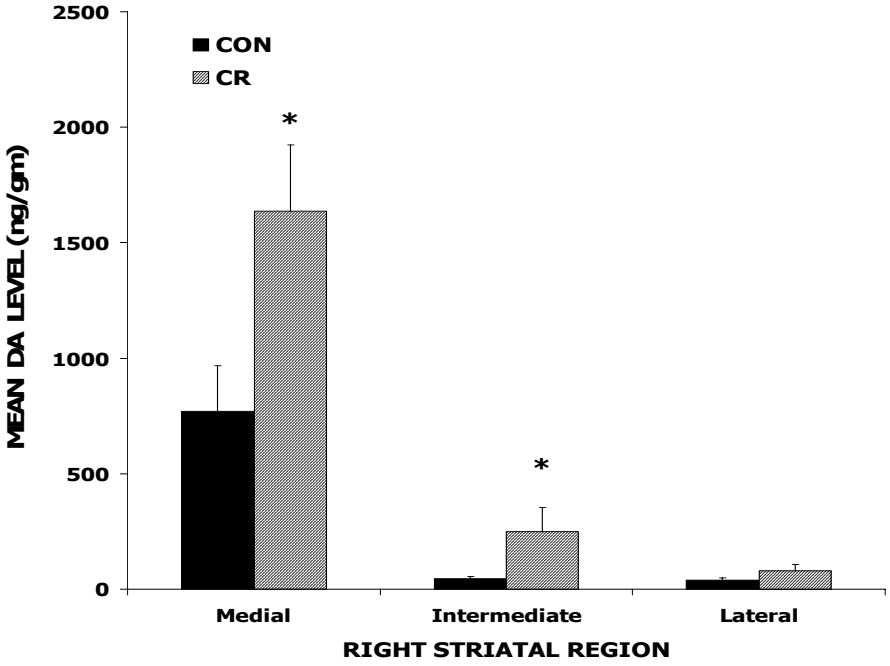


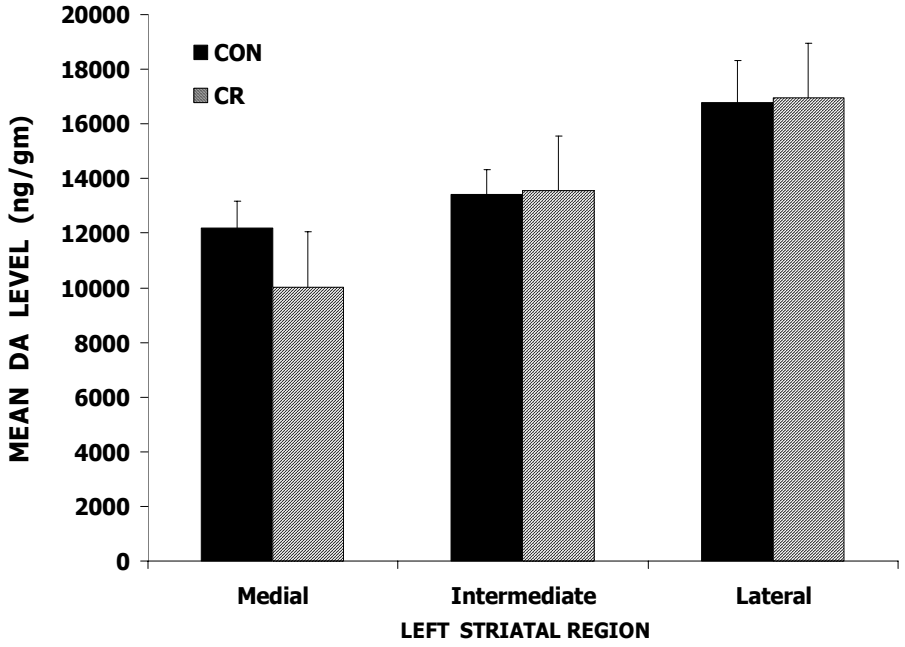
William Dauer[1,3] and Serge Przedborski[1,2,4,*]

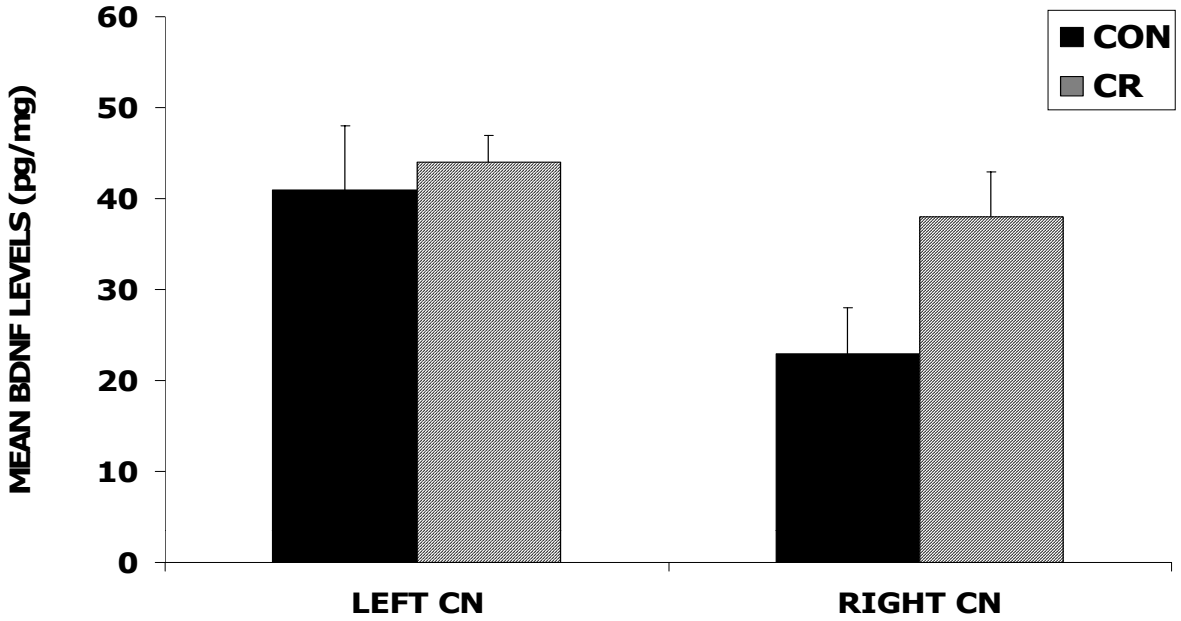

MEAN DISTANCE MOVED(cm)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
CON
CR
*
PRE-MPTP
POST-MPTP

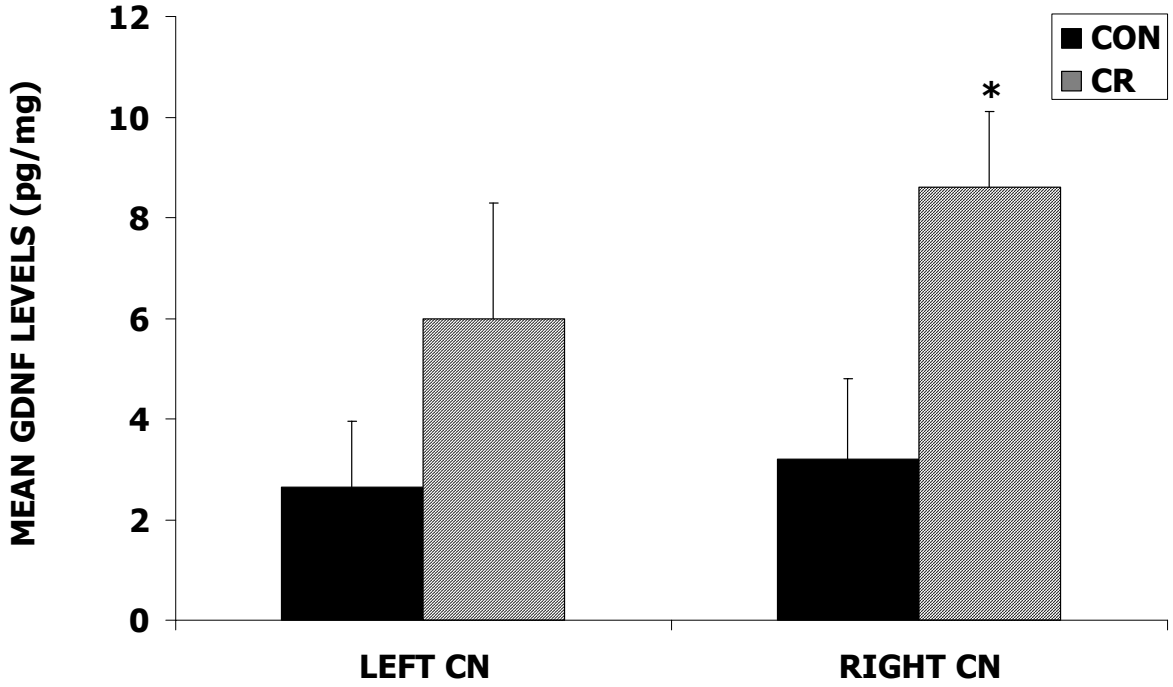

MOVEMENT SPEED(cm/sec)
10
9
8
7
6
5
4
3
2
1
0
CON
CR
*
PRE-MPTP
POST-MPTP


LV
Cd
Lat.
Int.
Med.
Put
Acb

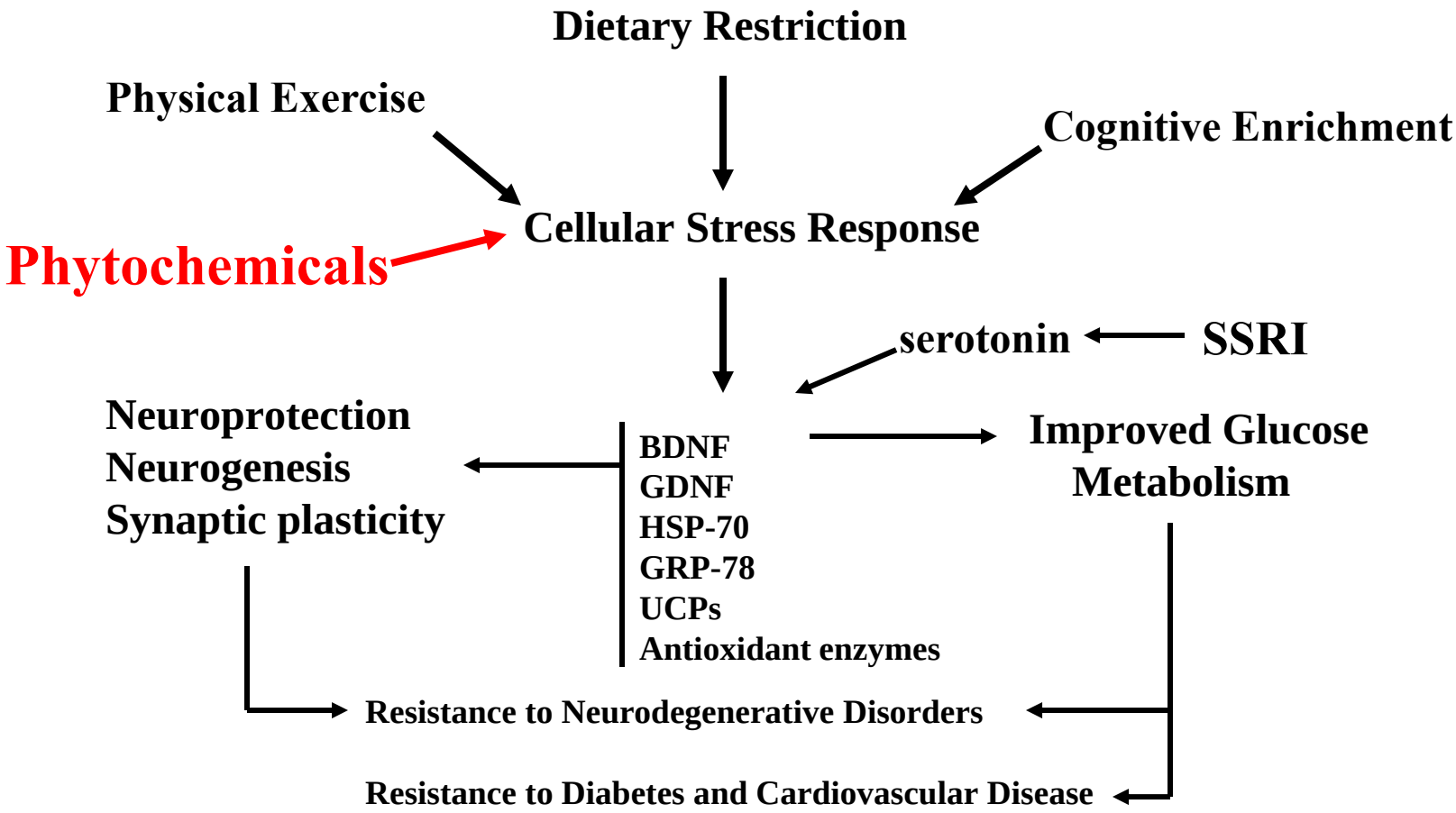

2500
2000
1500
1000
500
0
CON
CR
*
*
MEAN DA LEVEL (ng/gm)
Medial
Intermediate
Lateral
RIGHT STRIATAL REGION


20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
CON
CR
MEAN DA LEVEL (ng/gm)
Medial
Intermediate
Lateral
LEFT STRIATAL REGION


MEAN BDNF LEVELS (pg/mg)
60
50
40
30
20
10
0
CON
CR
LEFT CN
RIGHT CN


MEAN GDNF LEVELS (pg/mg)
12
10
8
6
4
2
0
CON
CR
*
LEFT CN
RIGHT CN

Dietary and Behavioral Neurohormesis



Resveratrol

Sulforaphane

Curcumin

Catechins

Allicin

Hypericin

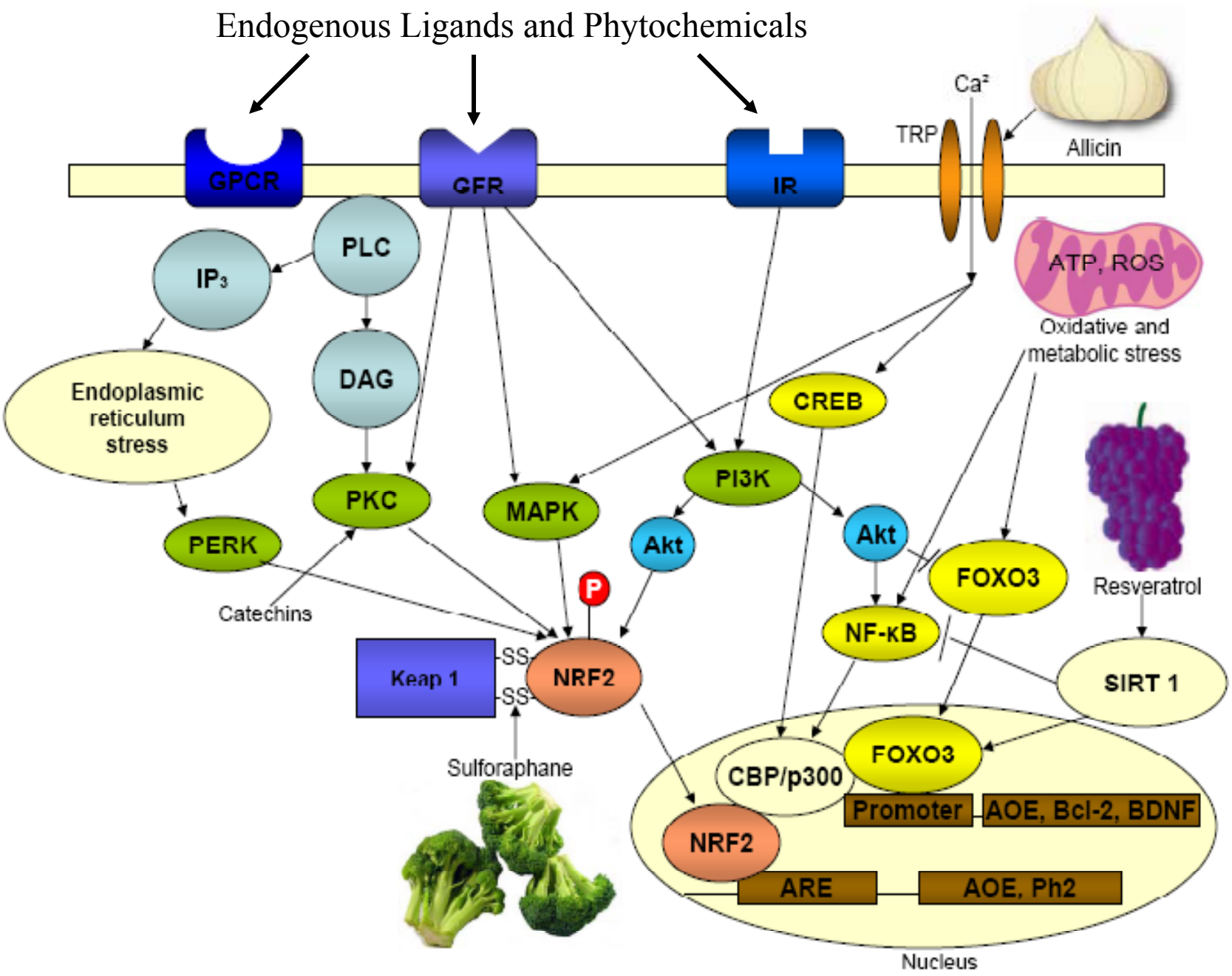
Vinceti M et al. Adverse health effects of selenium in humans. Rev Environ Health. 2001; 16:233-51.

Flores-Mateo G et al. Selenium and coronary heart disease: a meta-analysis. Am J Clin Nutr. 2006; 84:762-73.

Auger J. High-performance liquid chromatographic-inductively coupled plasma mass spectrometric evidence for Se-"alliins" in garlic and onion grown in Se-rich soil. J Chromatogr A. 2004; 1032:103-7.

Shaw JM. Suspected cyanide poisoning in two goats caused by ingestion of crab apple leaves and fruits. Vet Rec. 1986; 119:242-3.

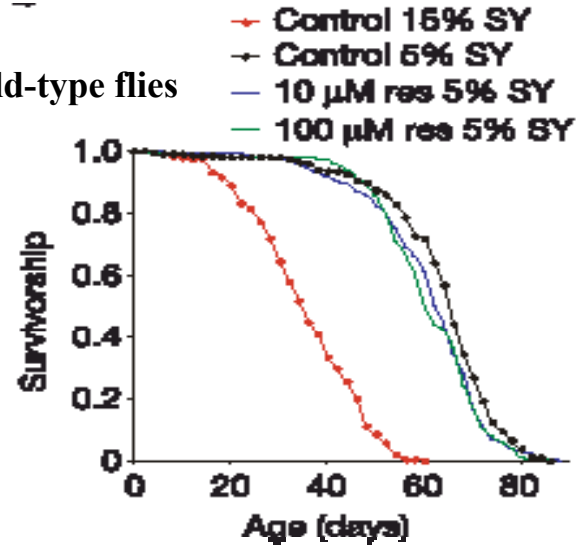
Tchantchou F et al. Apple juice concentrate prevents oxidative damage and impaired maze performance in aged mice. J Alzheimers Dis. 2005; 8: 283-7.


Endogenous Ligands and Phytochemicals
GPCR
GFR
IR
Ca²
TRP
Allicin
PLC
IP3
DAG
ATP, ROS
Oxidative and metabolic stress
Endoplasmic reticulum stress
CREB
PI3K
PKC
MAPK
Akt
Akt
PERK
FOXO3
Resveratrol
Catechins
P
NF-κB
Keap 1
SS
SS
NRF2
SIRT 1
Sulforaphane
CBP/p300
FOXO3
Promoter
AOE, Bcl-2, BDNF
NRF2
ARE
AOE, Ph2
Nucleus

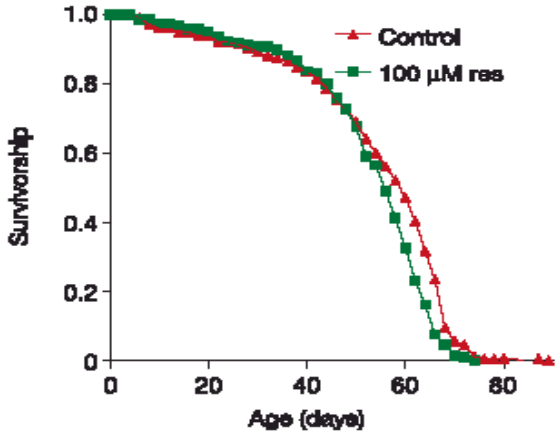
Sirtuin activators mimic caloric restriction and delay ageing in metazoans

Jason G. Wood[1]*, Blanka Rogina[2]*, Siva Lavu[1], Konrad Howitz[3], Stephen L. Helfand[2], Marc Tatar[4] & David Sinclair[1]

Wild-type flies

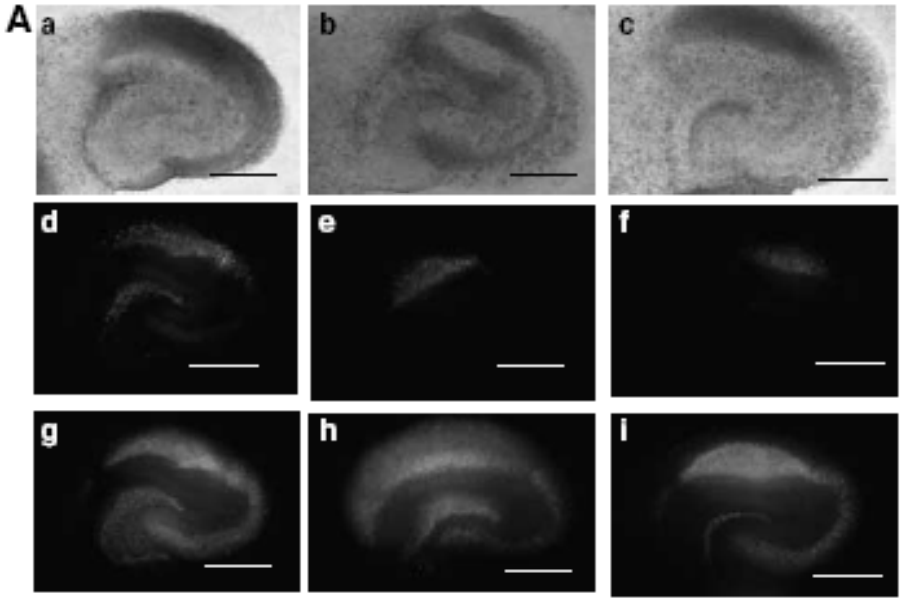


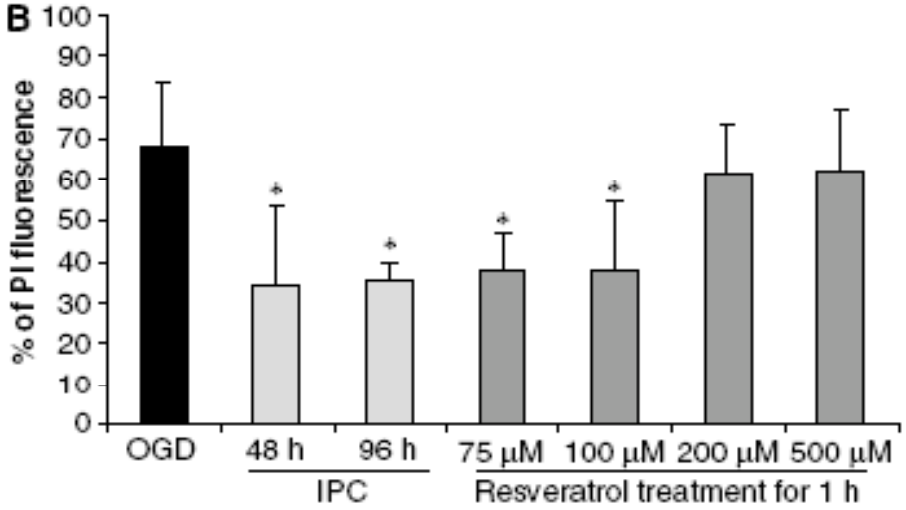
Sir-2 mutant flies



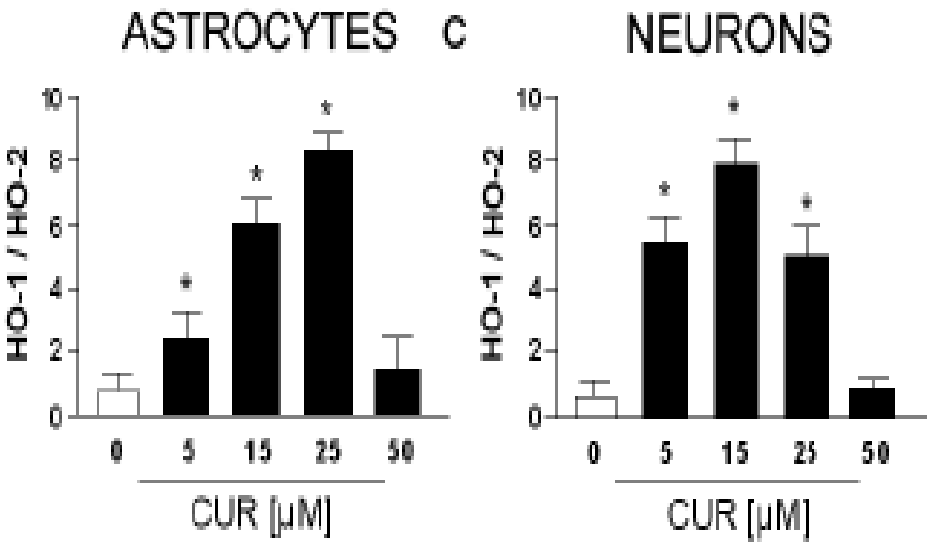
Resveratrol mimics ischemic preconditioning in the brain

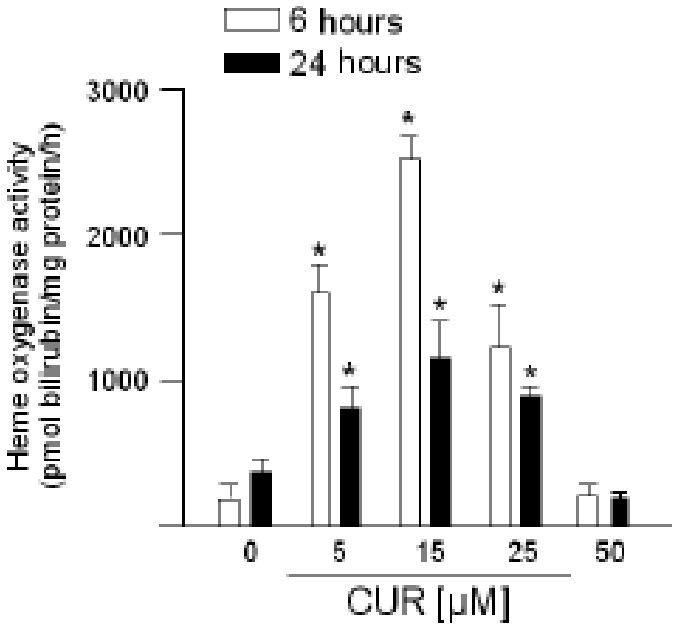
Ami P Raval[1], Kunjan R Dave[1] and Miguel A Pérez-Pinzón





Curcumin induces expression of HO-1 in astrocytes and neurons with a bi-phasic dose-response

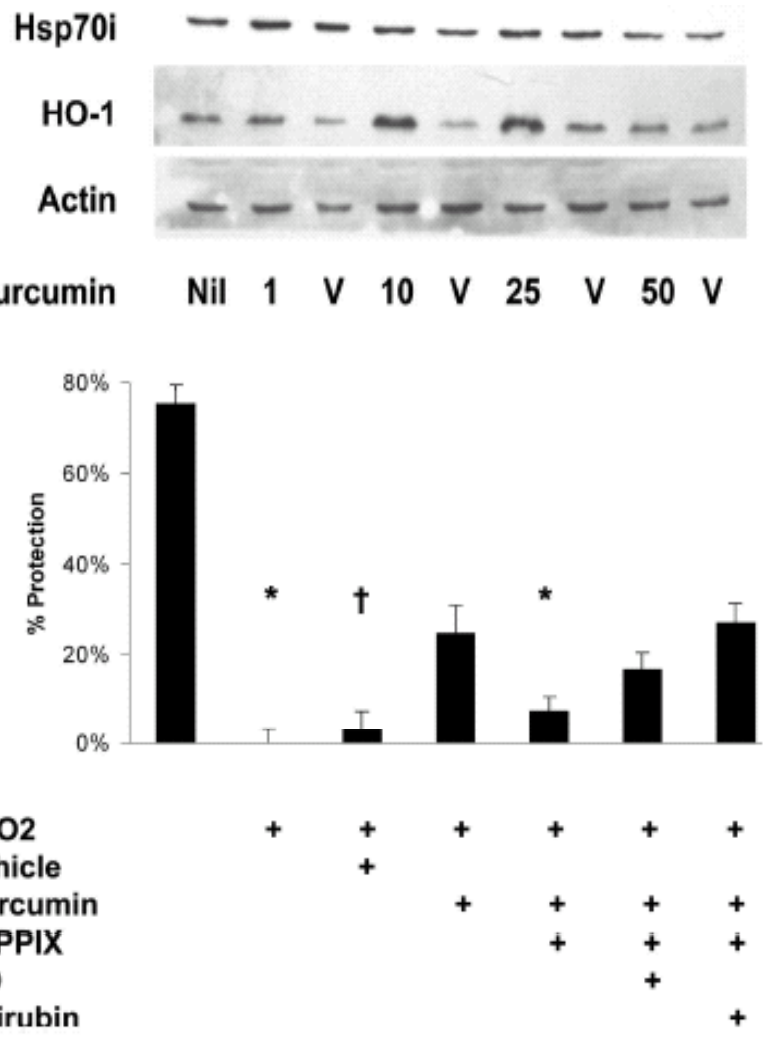




SCAPAGNINI ET AL.

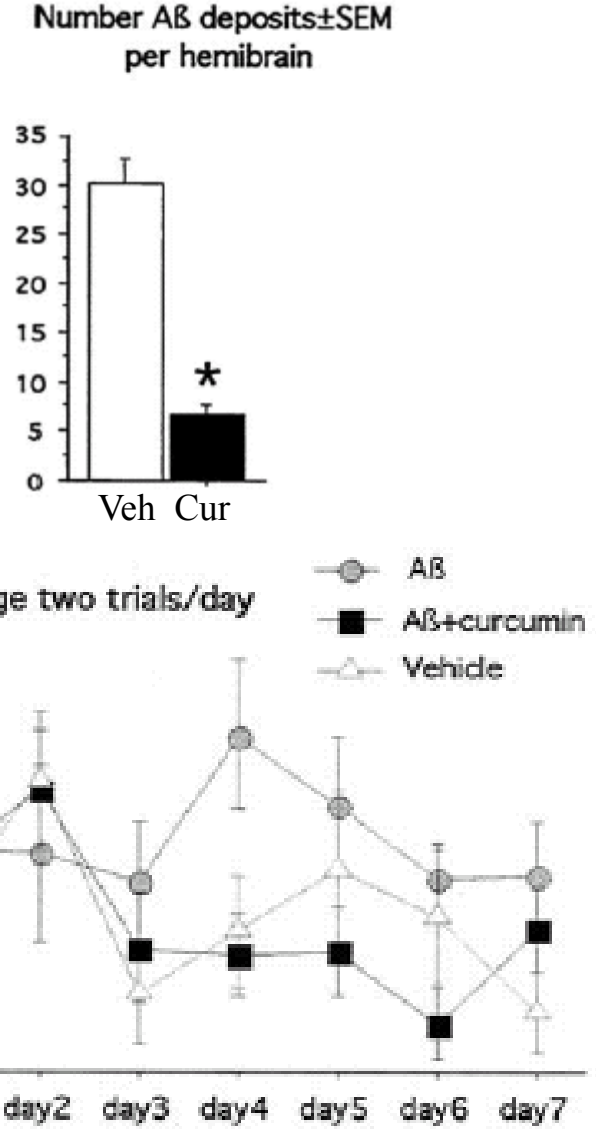
Curcumin Induces Heme Oxygenase-1 in Hepatocytes and Is Protective in Simulated Cold Preservation and Warm Reperfusion Injury

Stephen J. McNally, Ewen M. Harrison, James A. Ross, O. James Garden, and Stephen J. Wigmore



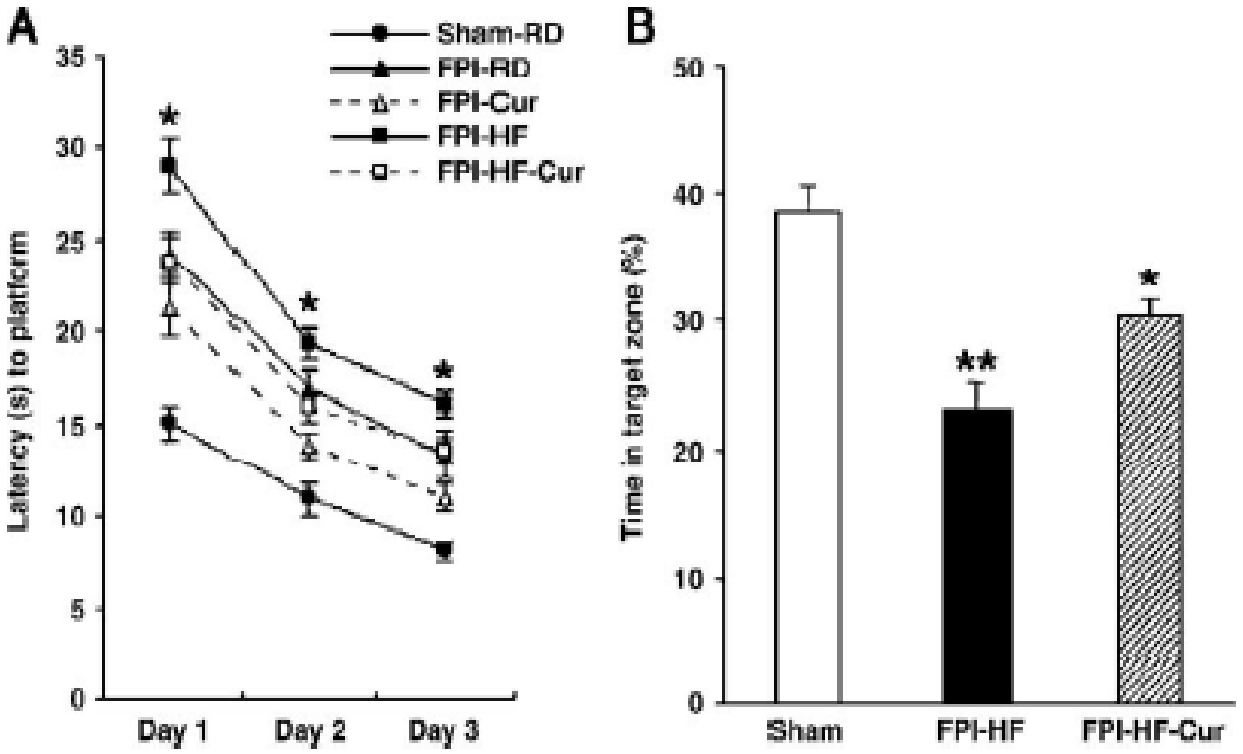
Phenolic anti-inflammatory antioxidant reversal of Aβ-induced cognitive deficits and neuropathology

S.A. Frautschy*, W. Hu, P. Kim, S.A. Miller, T. Chu, M.E. Harris-White, G.M. Cole

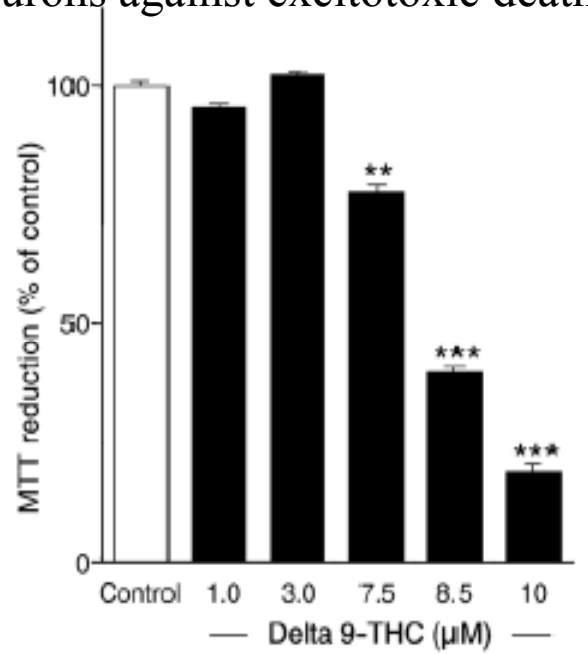


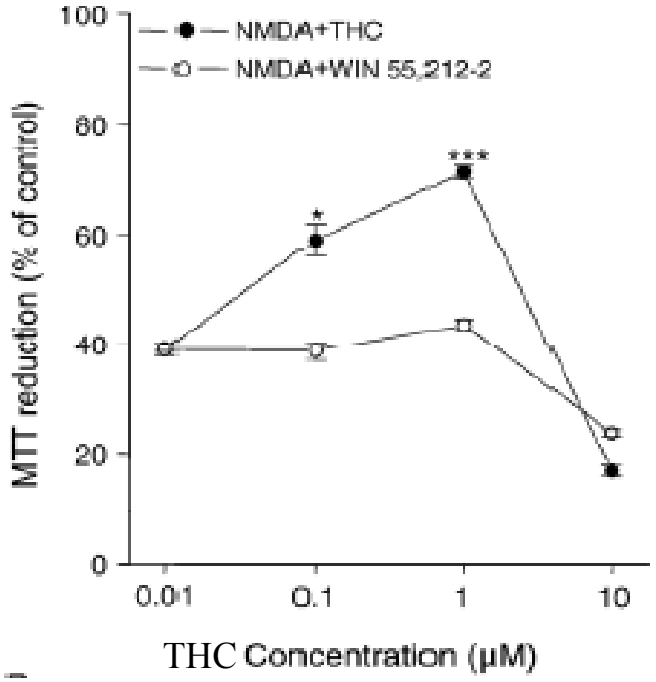
Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition

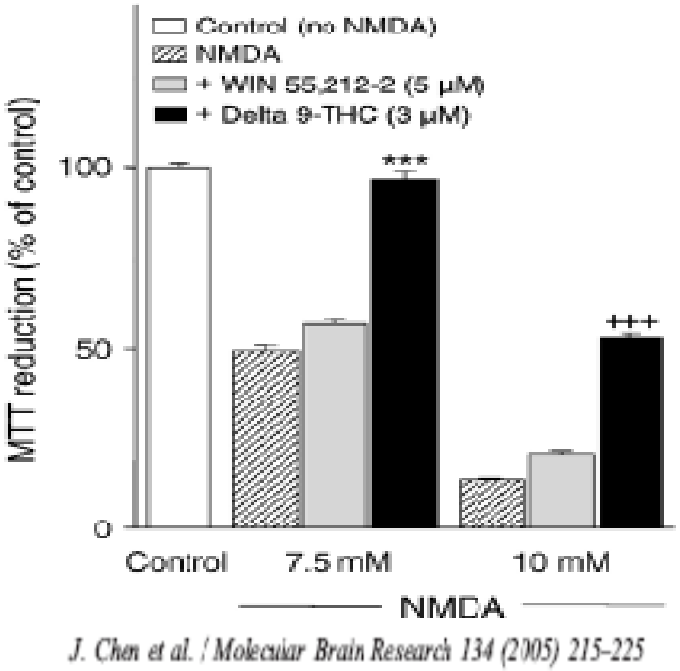
Aiguo Wu [a], Zhe Ying [a], Fernando Gomez-Pinilla [a,b,*]



Subtoxic doses of THC protect neurons against excitotoxic death

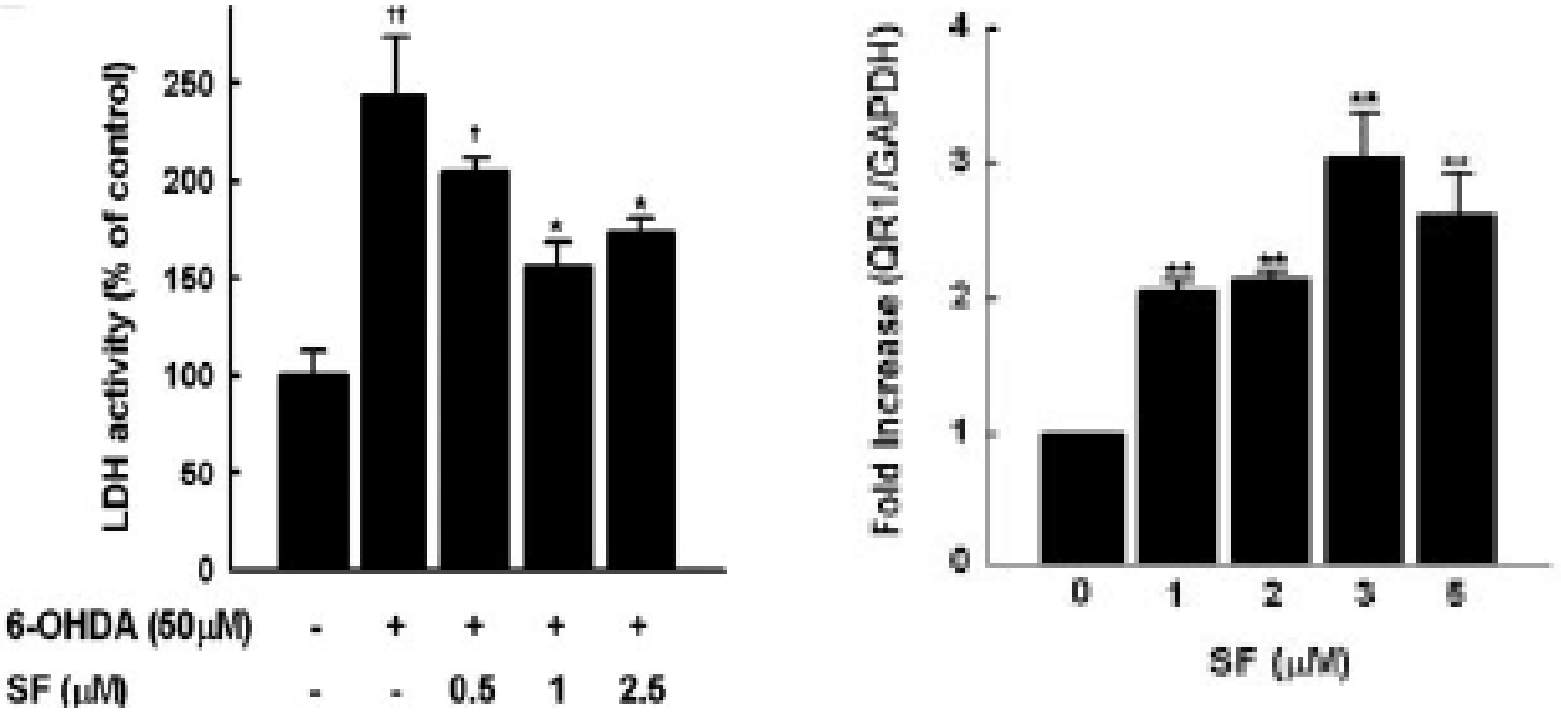






J. Chen et al. / Molecular Brain Research 134 (2005) 215–225

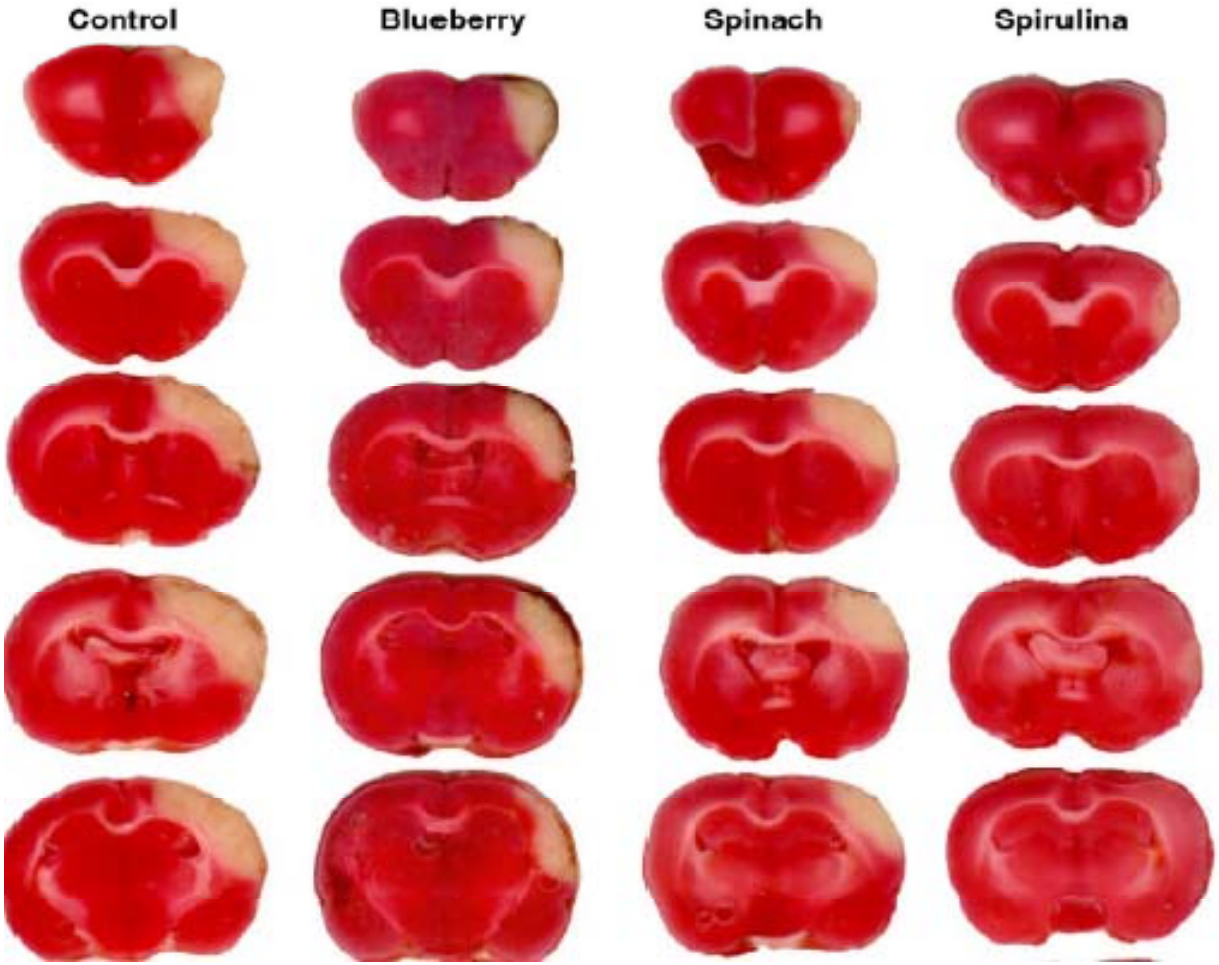
Sulforaphane is neuroprotective in an experimental model of Parkinson's disease



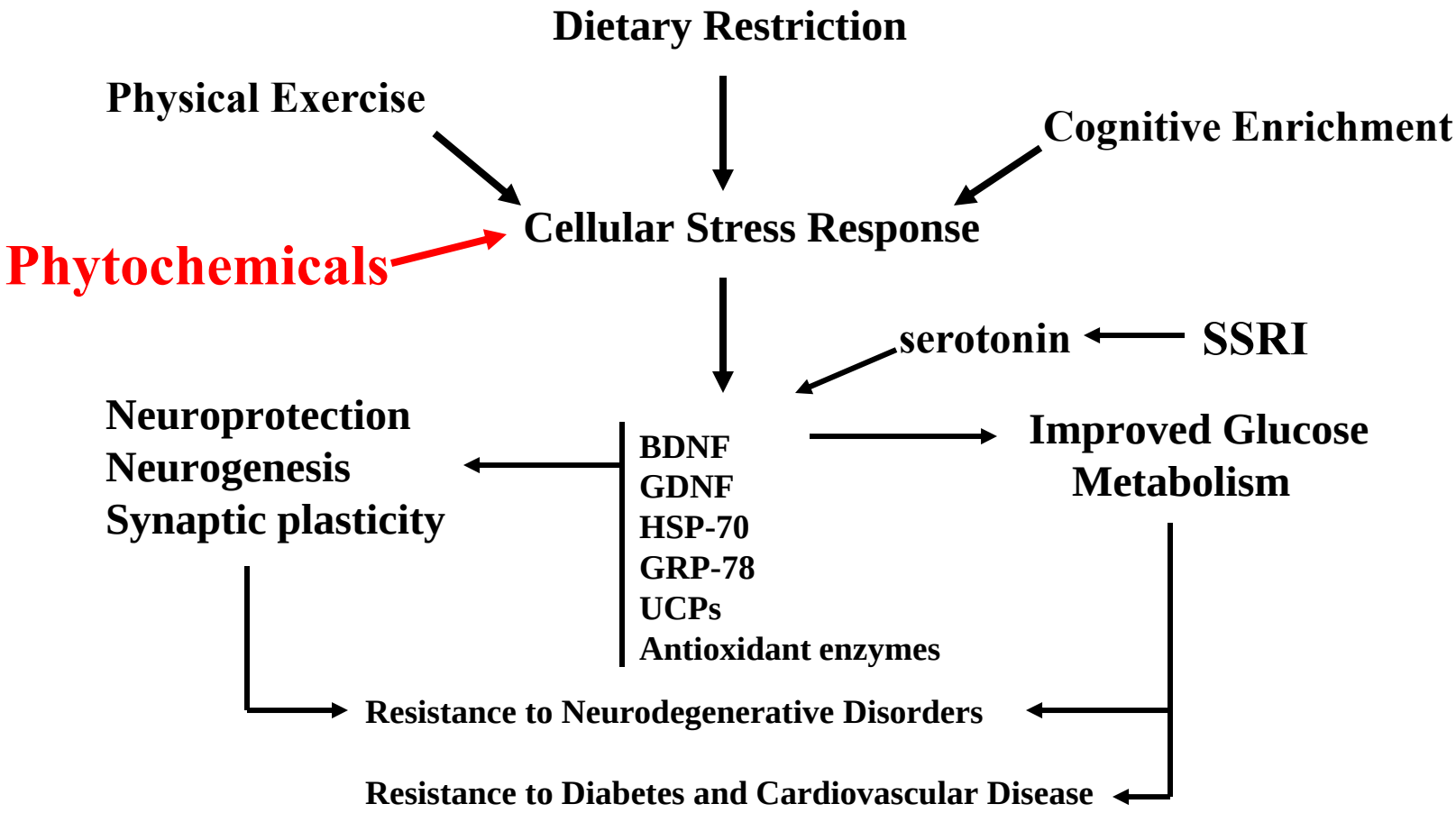
Han et al.

Dietary supplementation with blueberries, spinach, or spirulina reduces ischemic brain damage

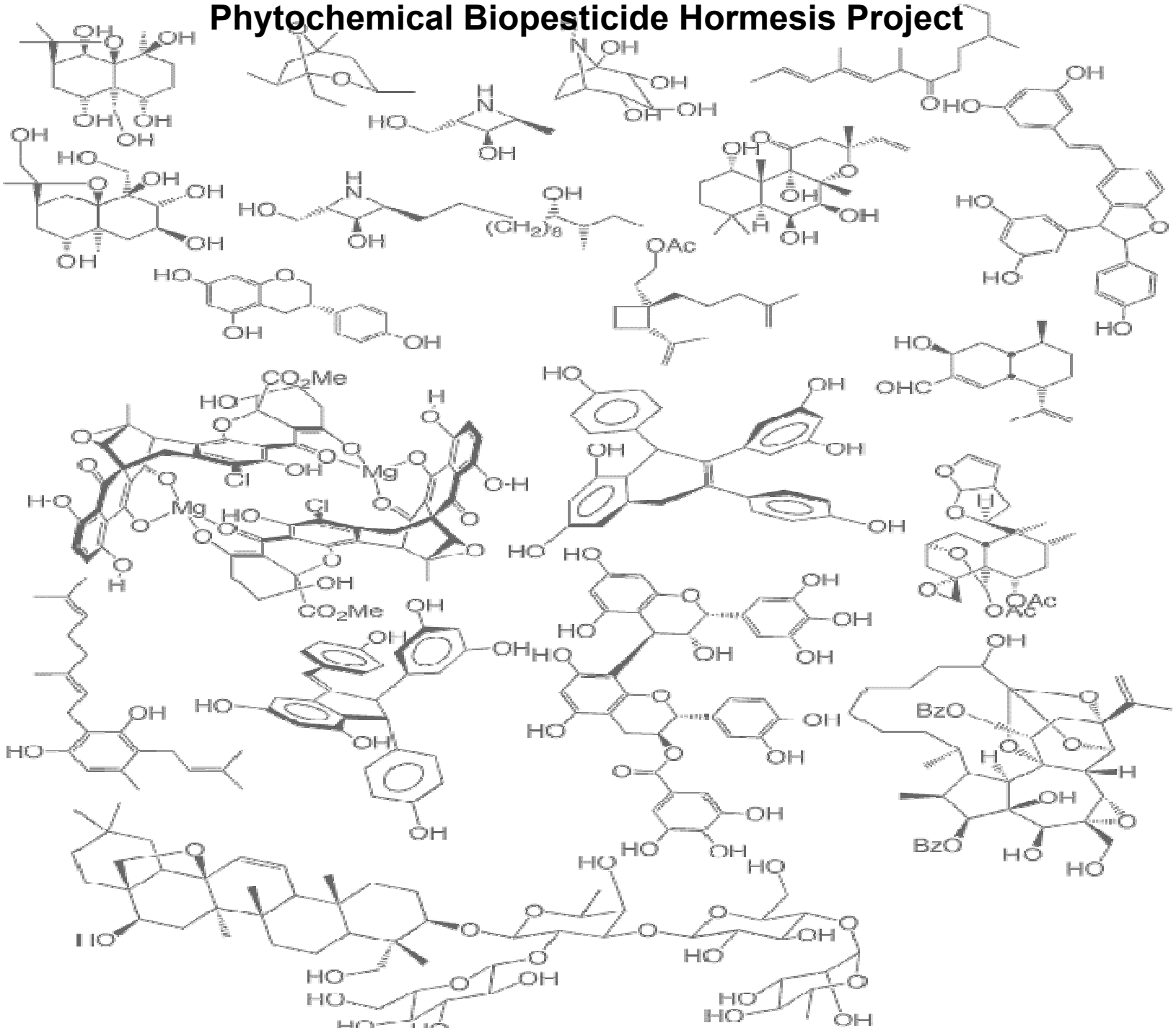
Yun Wang[a], Chen-Fu Chang[a], Jenny Chou[a], Hui-Ling Chen[a], Xiaolin Deng[a], Brandon K. Harvey[a], Jean Lud Cadet[a], Paula C. Bickford[b,*]

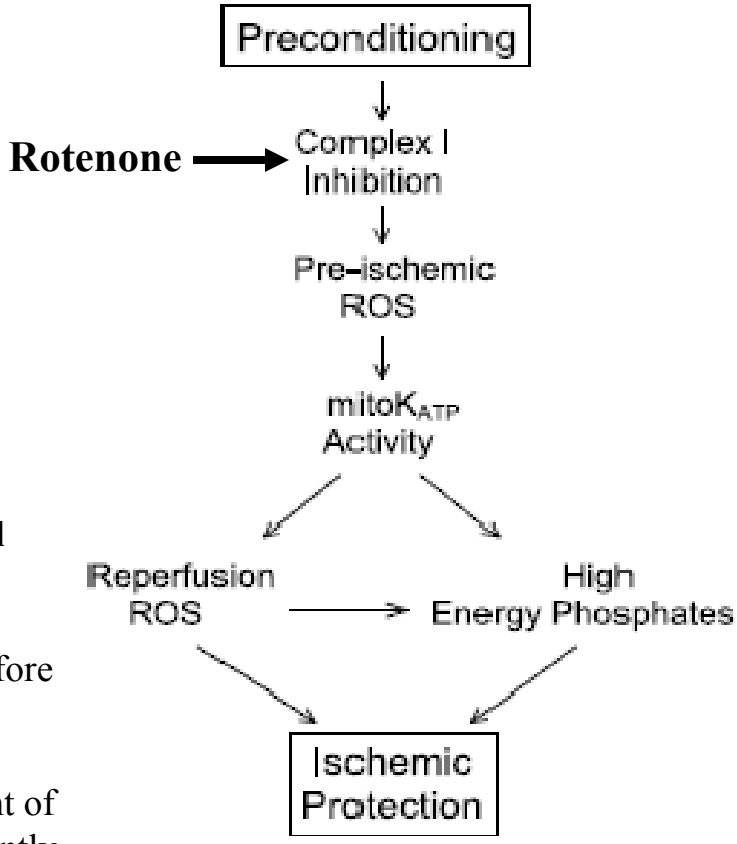


Dietary and Behavioral Neurohormesis



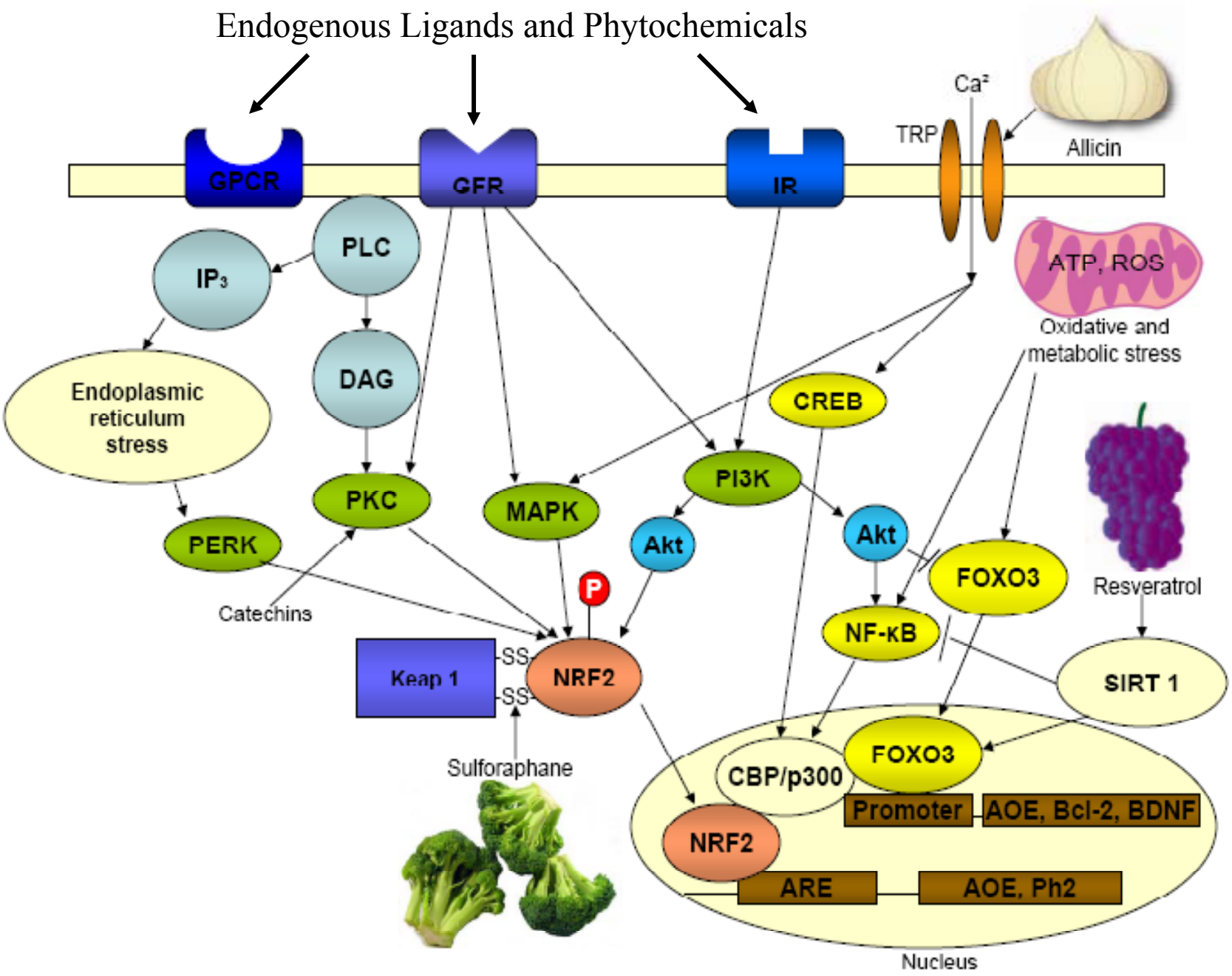
Phytochemical Biopesticide Hormesis Project





Rotenone, a mitochondrial electron transport inhibitor, ameliorates ischemia-reperfusion-induced intestinal mucosal damage in rats. Ichikawa et al. (2004) Redox Rep. 9:313-316.

Rotenone at a dose of 100 mg/kg was given to rats orally 2 h before the ischemia. Intraluminal hemoglobin and protein levels, the mucosal content of thiobarbituric acid-reactive substances (TBARS), the mucosal myeloperoxidase activity, and the content of inflammatory cytokines (CINC-1, TNF-alpha) were all significantly increased from mean basal levels after 60 min of reperfusion. These increases after I/R were inhibited by treatment with rotenone at a dose of 100 mg/kg. This investigation suggests that rotenone has potential as a new therapeutic agent for reperfusion injury.


Endogenous Ligands and Phytochemicals
GPCR
GFR
IR
Ca²
TRP
Allicin
PLC
IP3
DAG
ATP, ROS
Oxidative and metabolic stress
Endoplasmic reticulum stress
CREB
PI3K
PKC
MAPK
Akt
Akt
PERK
FOXO3
Resveratrol
Catechins
P
NF-κB
Keap 1
SS
SS
NRF2
SIRT 1
Sulforaphane
CBP/p300
FOXO3
Promoter
AOE, Bcl-2, BDNF
NRF2
ARE
AOE, Ph2
Nucleus