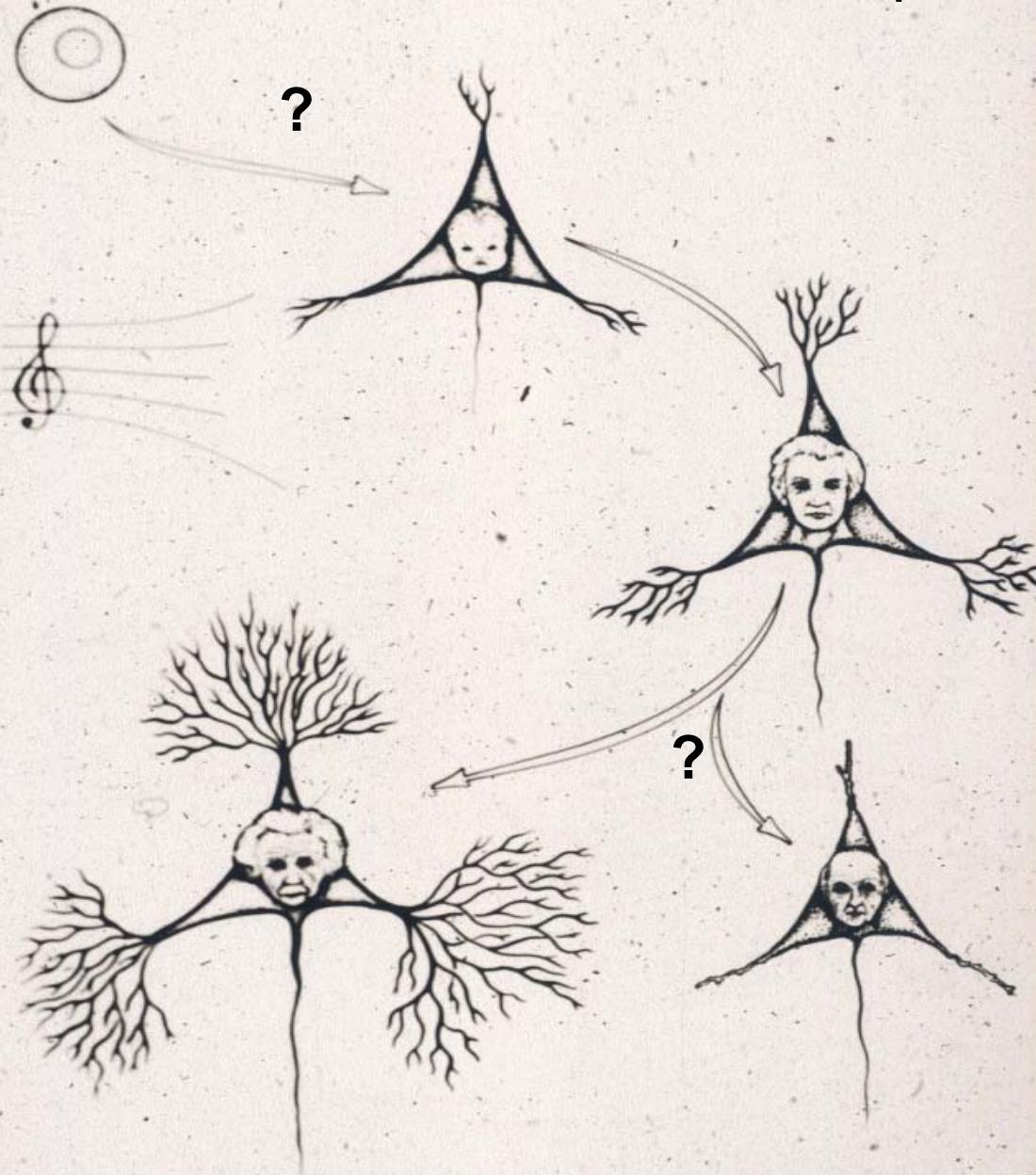


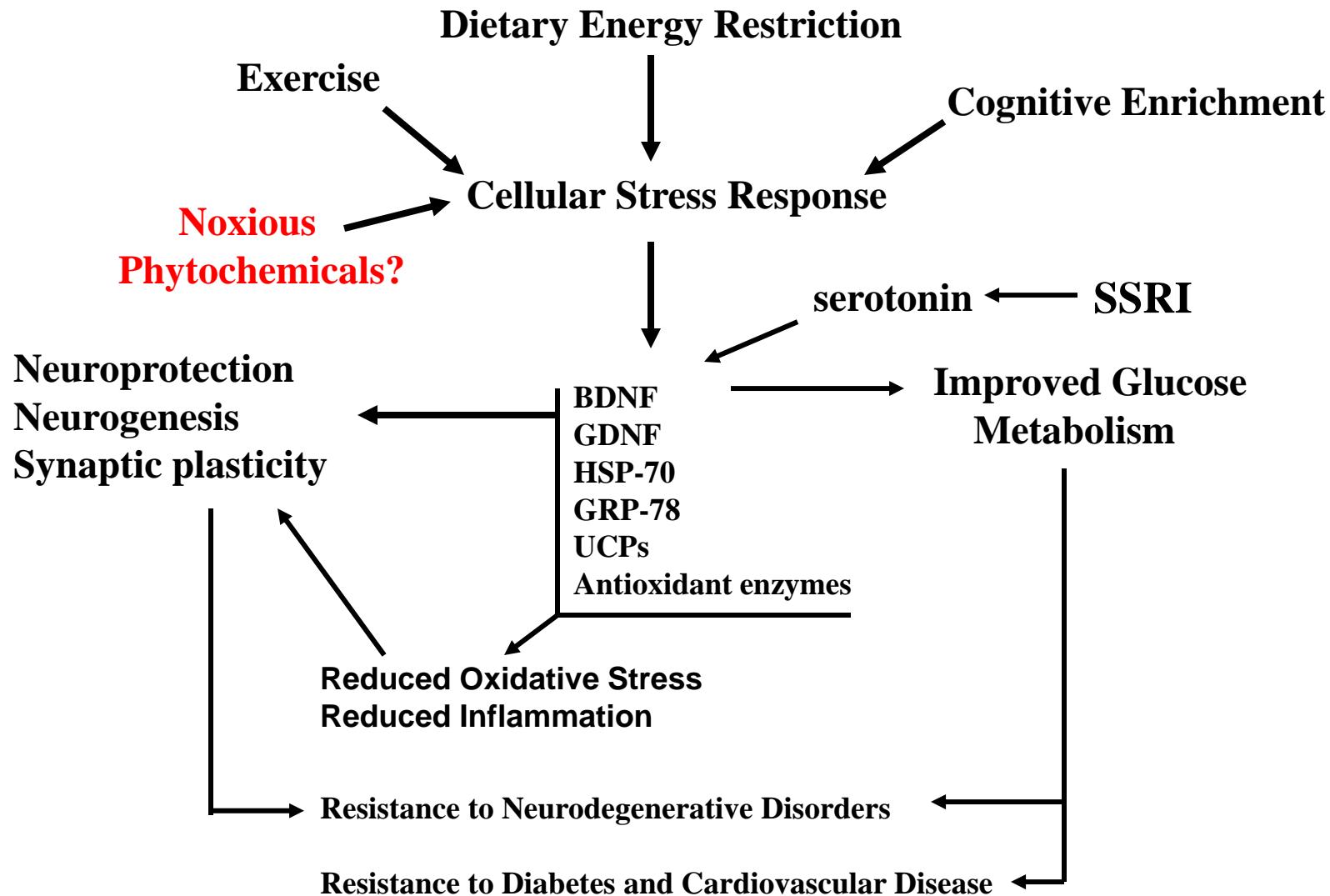
“Hormesis-Based Development of Botanical Insect Antifeedants as Neurotherapeutic Agents?”

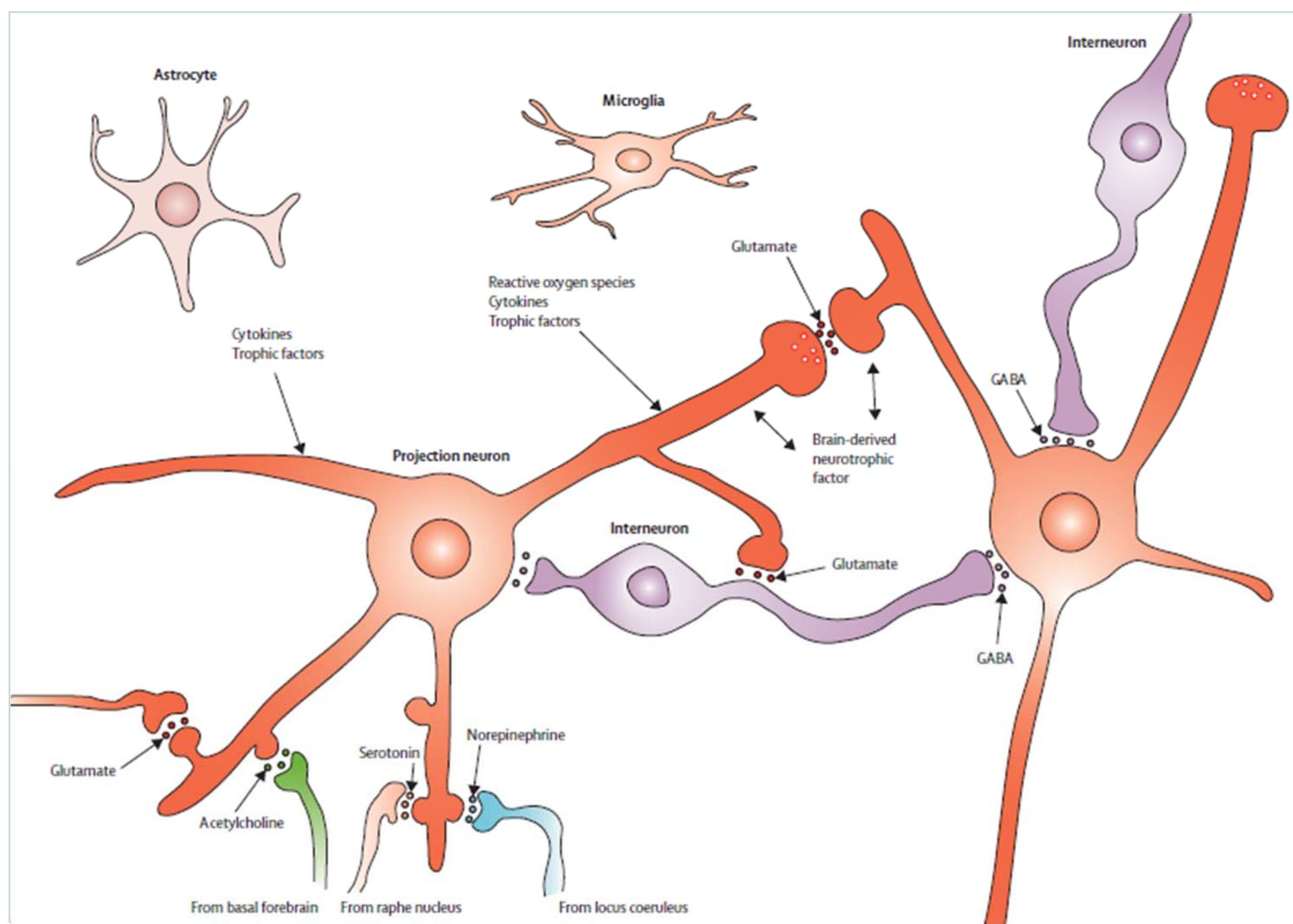


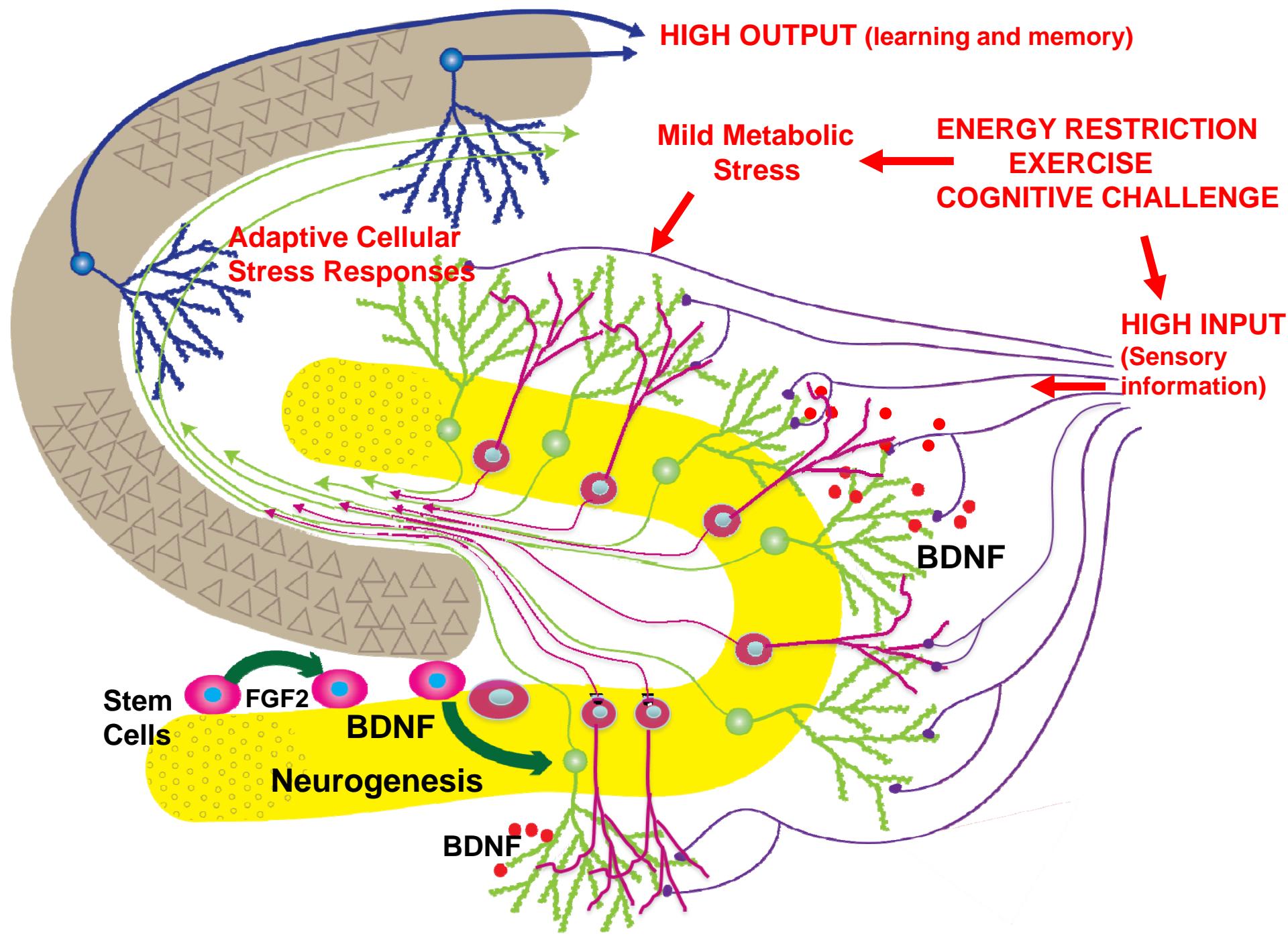
**National Institute on Aging
Intramural Research Program**

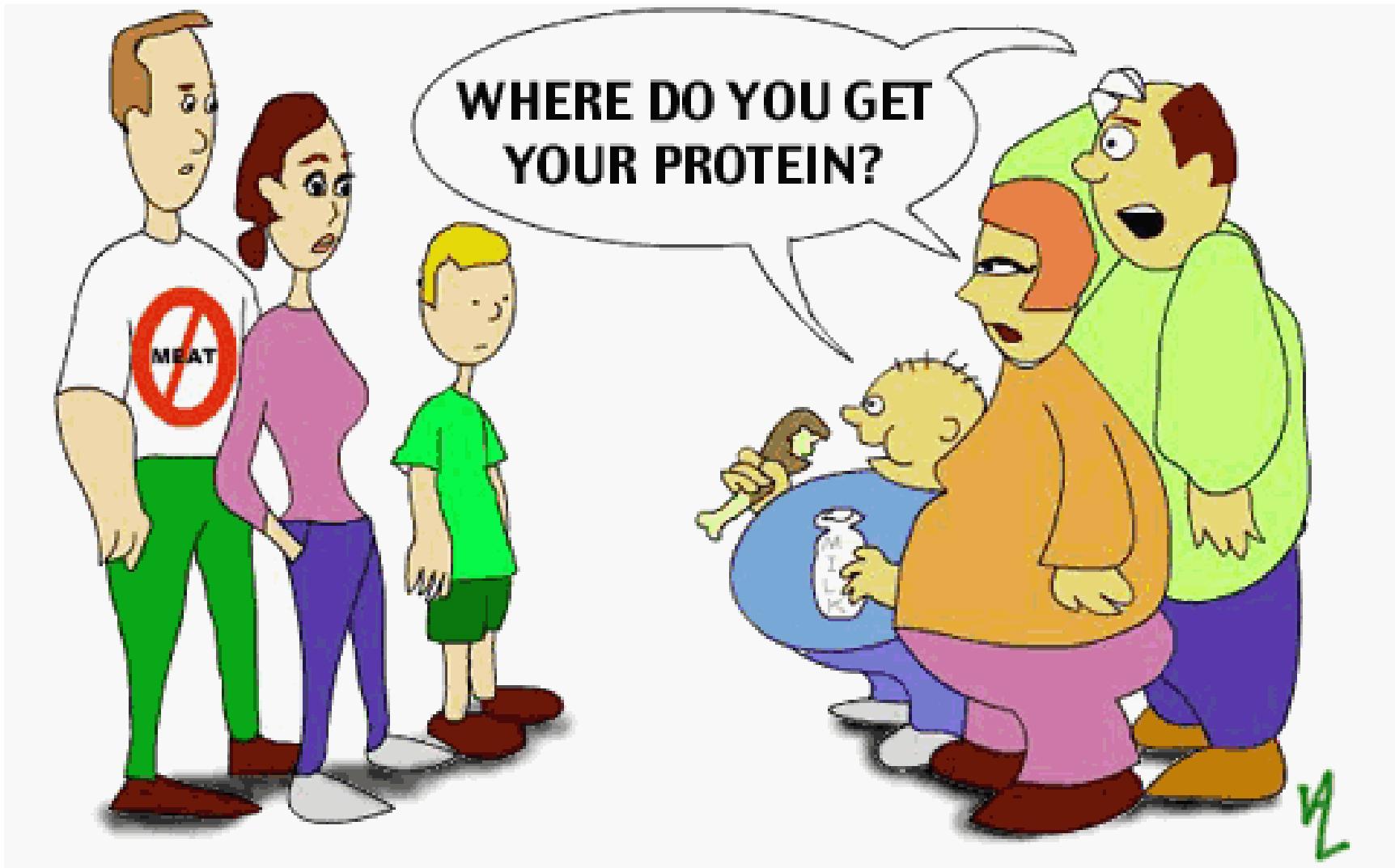
Laboratory of Neurosciences
CMNS – Mark Mattson
DDDS – Nigel Greig
IMGU – Cathy Wolkow
RPU – Stuart Maudsley
NBU – Henriette van Praag

The Hormesis Theory of Neuroprotection and Neurorestoration

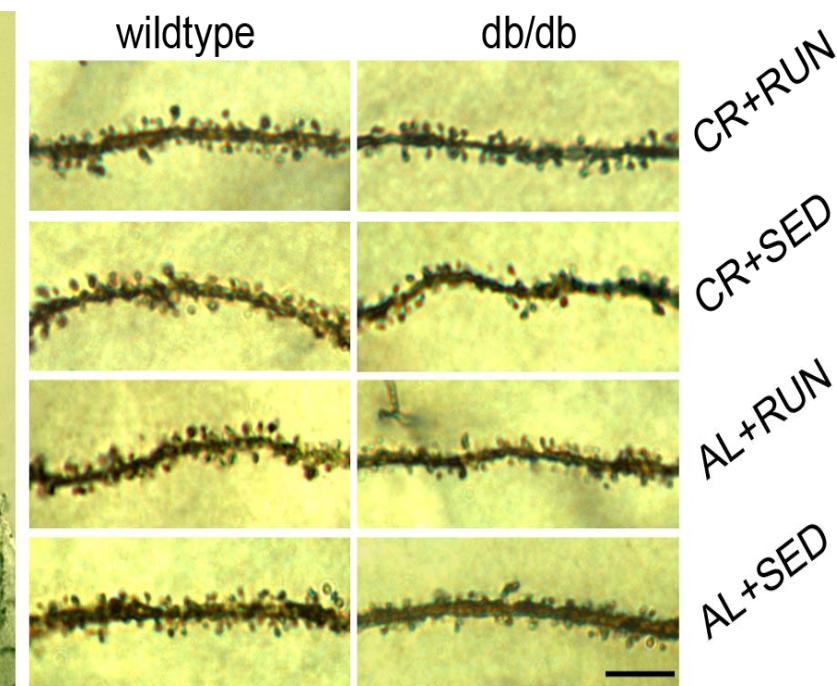




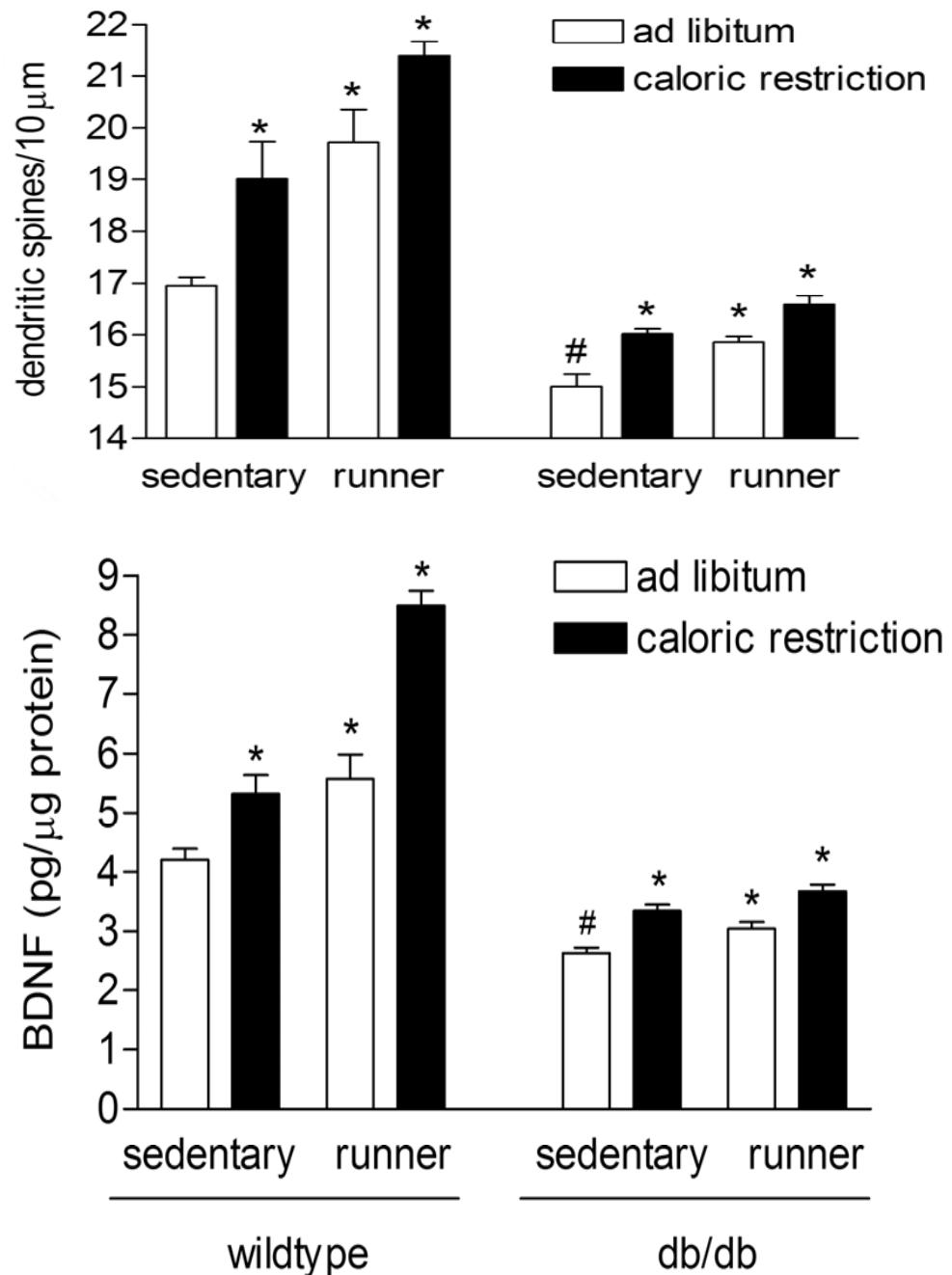


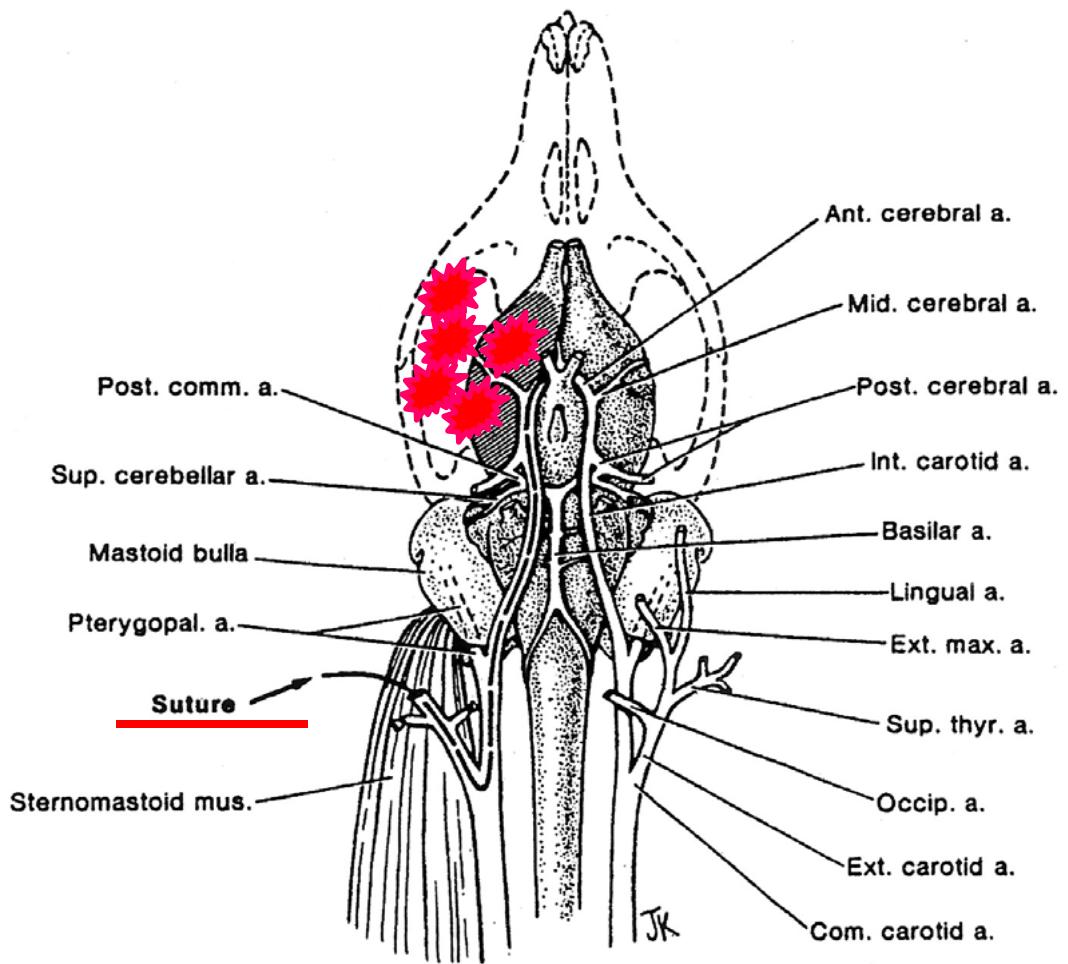


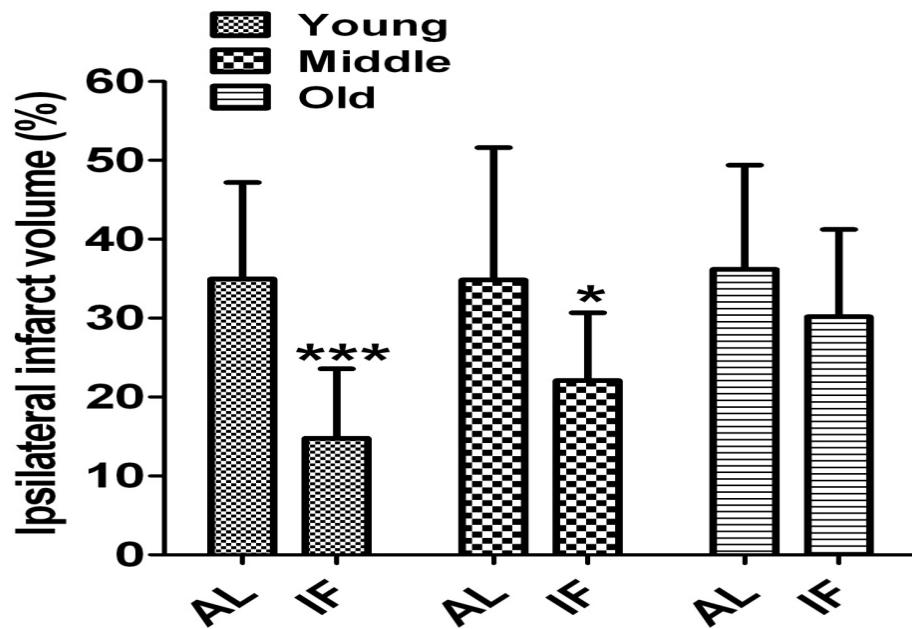
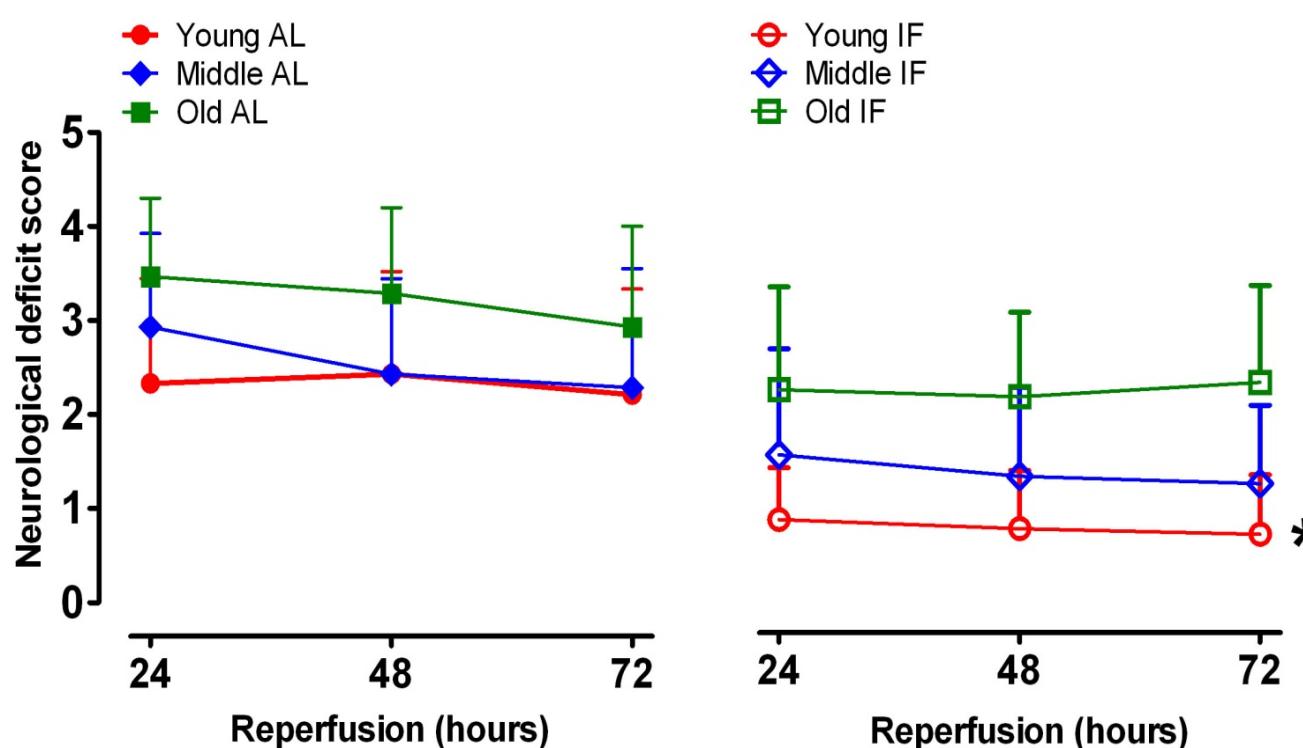
Martin B, Ji S, Maudsley S, Mattson MP (2010) “Control” laboratory rodents are metabolically morbid: Why it matters. *Proc Natl Acad Sci U S A*. 2010; 107(14):6127-33.



Stranahan et al. (2009)
Hippocampus 19: 951-961.

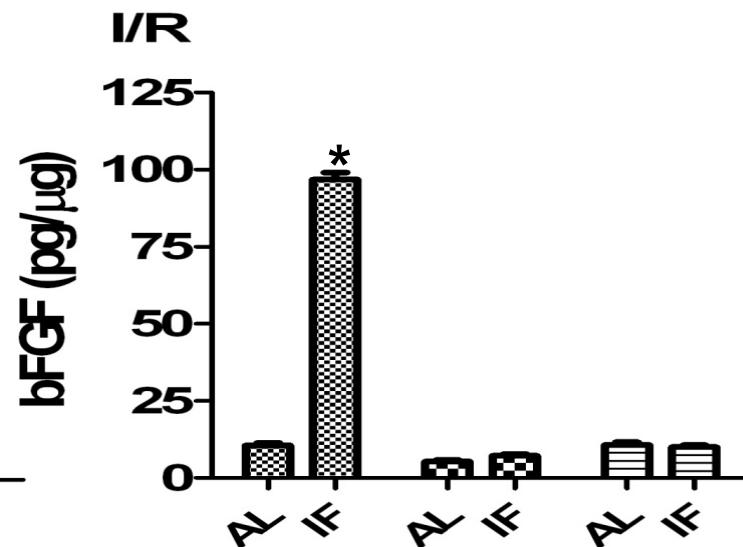
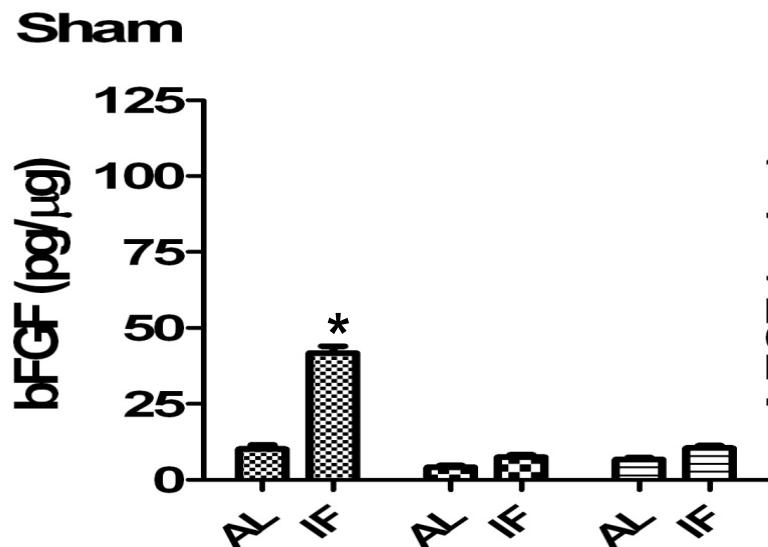
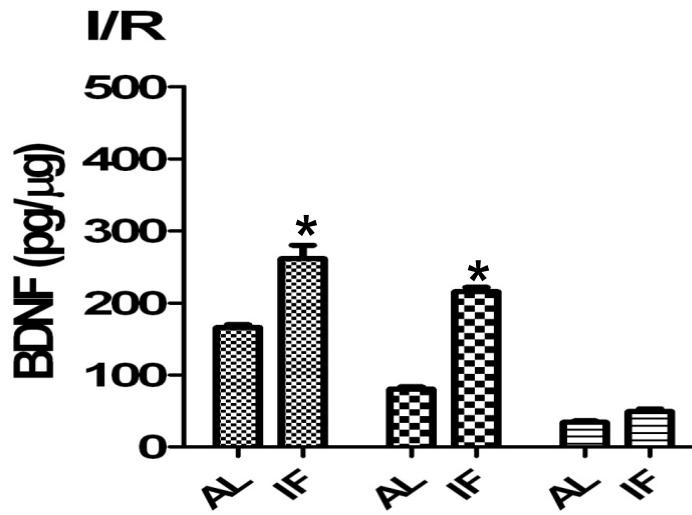
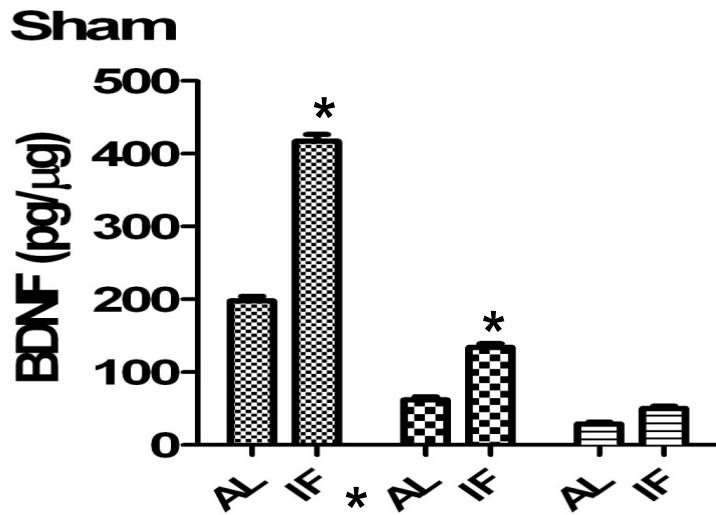


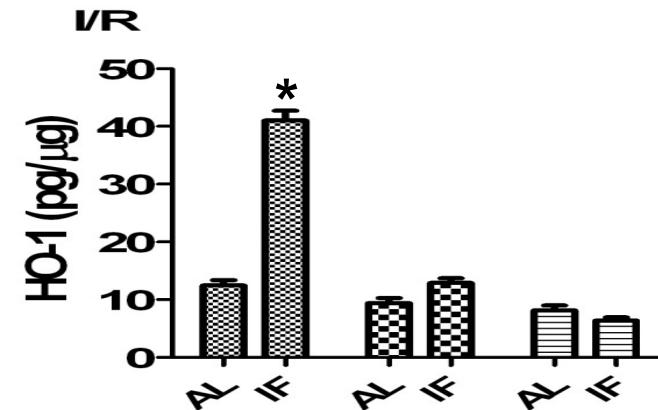
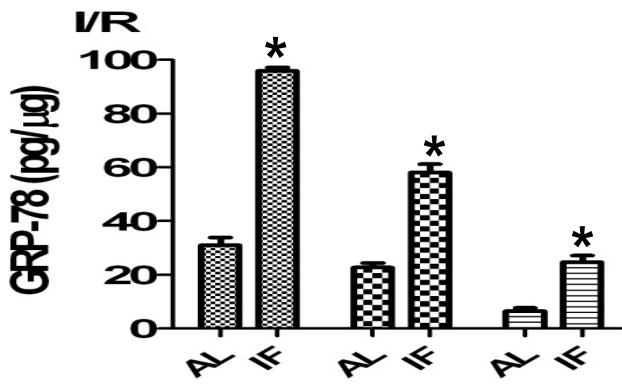
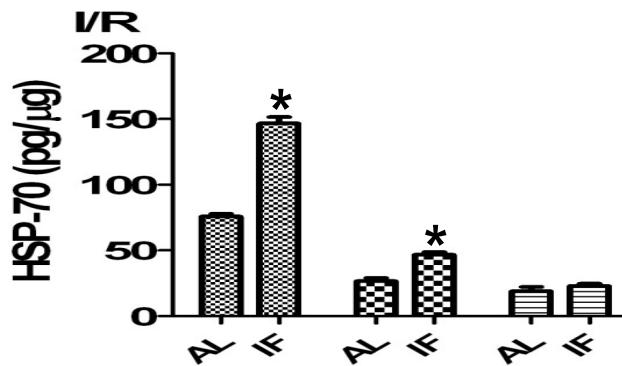
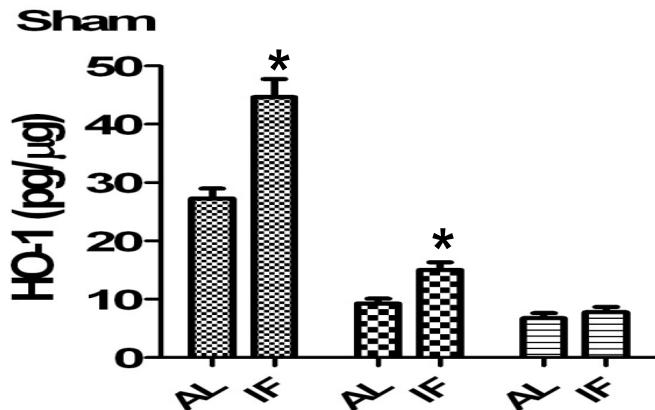
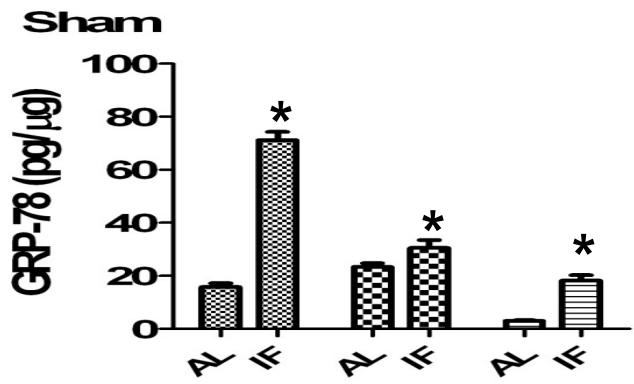
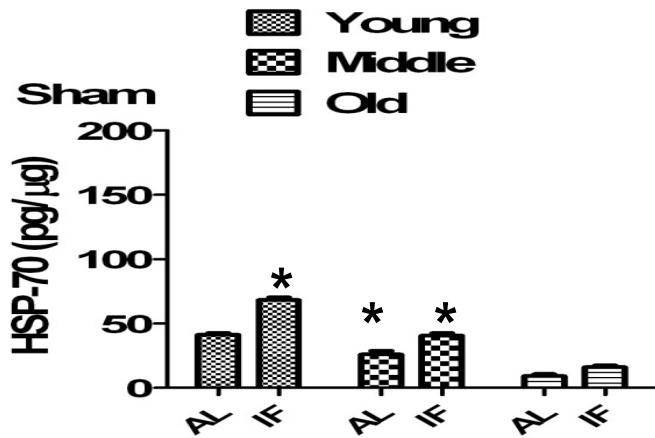




Arumugam, T. V. et al.
 (2009) Age and energy
 intake interact to modify
 cell stress pathways and
 stroke outcome. *Ann.
 Neurol.* 67(1):41-52.

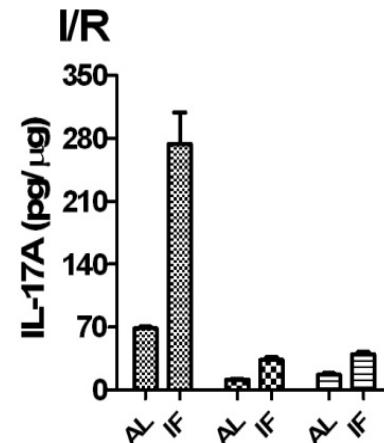
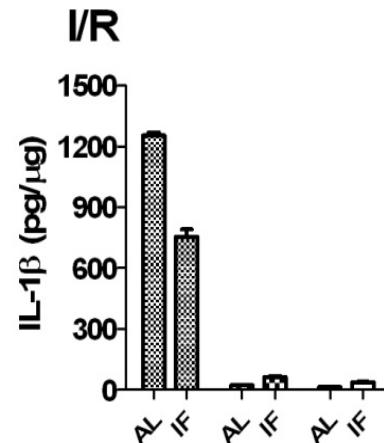
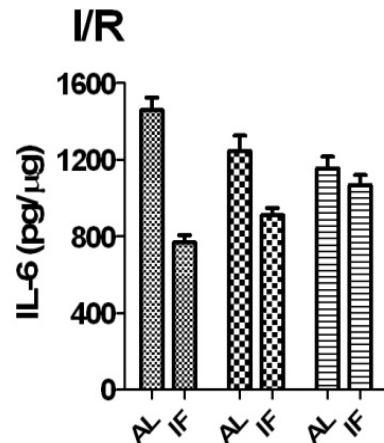
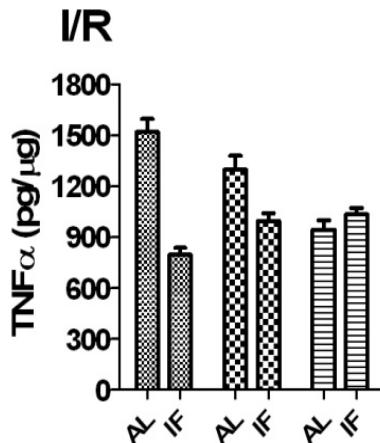
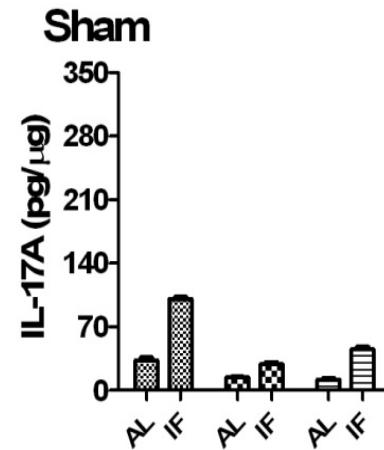
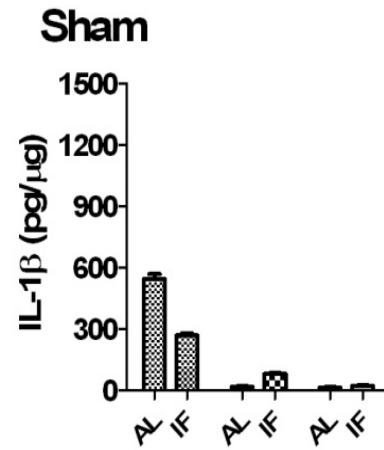
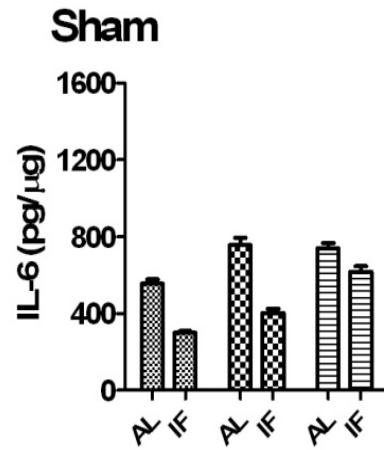
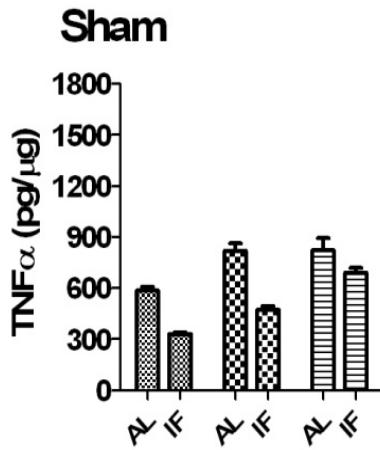
Young
Middle
Old



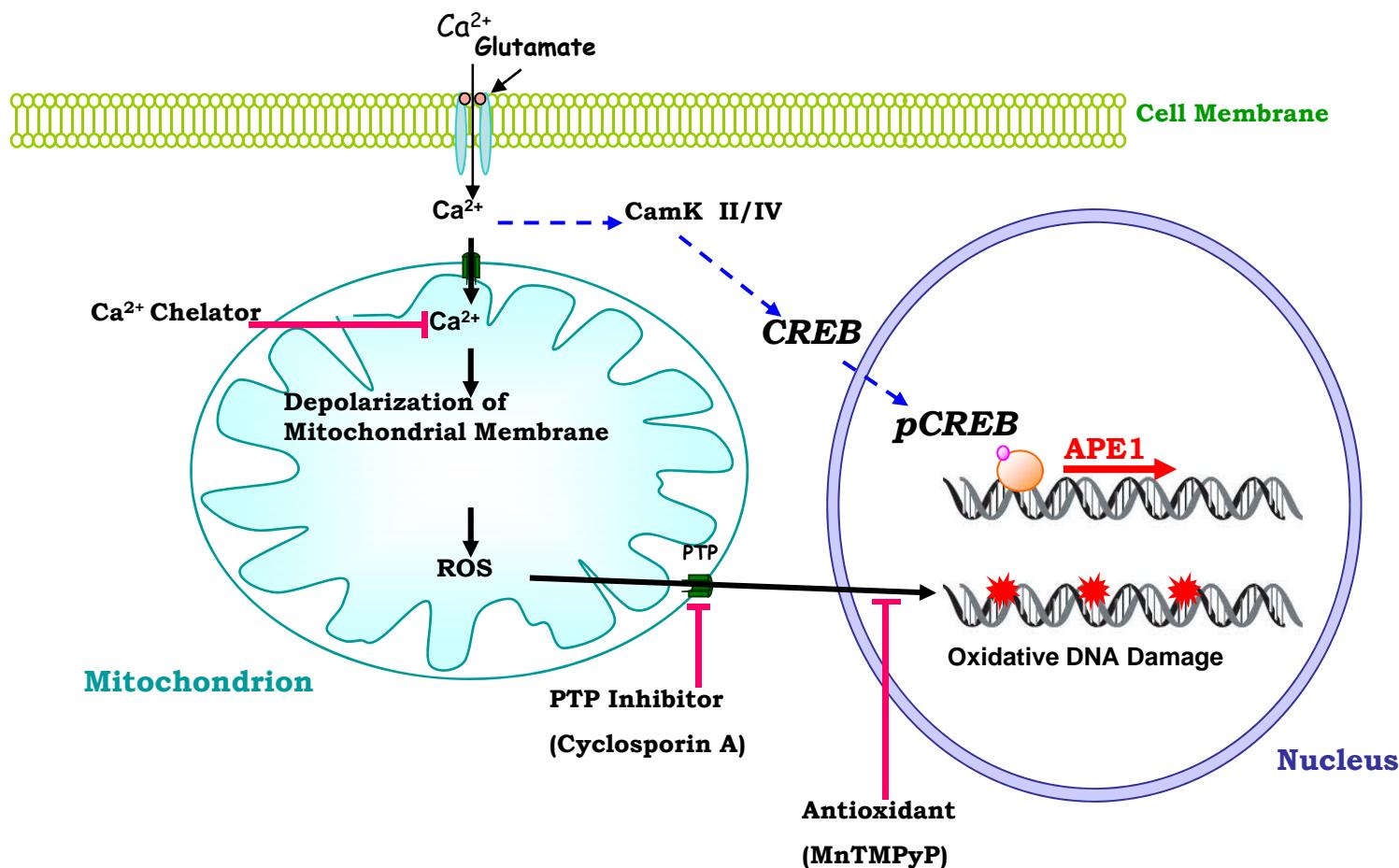


 **Young**
 **Middle**
 **Old**

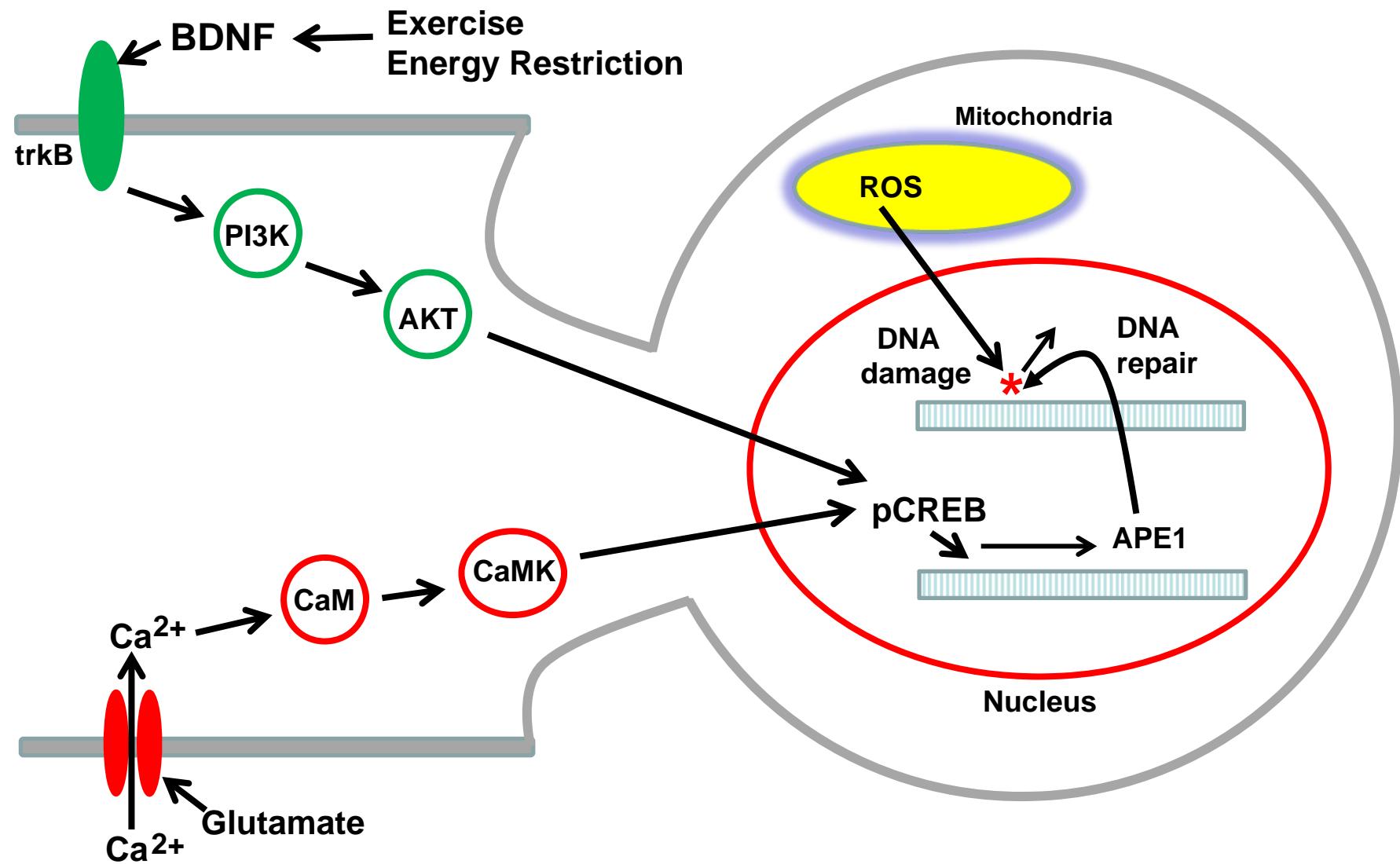
Conclusions: Alternate day fasting protects nerve cells against a stroke in young and middle-age mice, but not old mice. Apparently, the ability of brain cells to respond adaptively to fasting is impaired in old age as indicated by reduced levels of neurotrophic factors and cellular stress proteins, and increased inflammation.

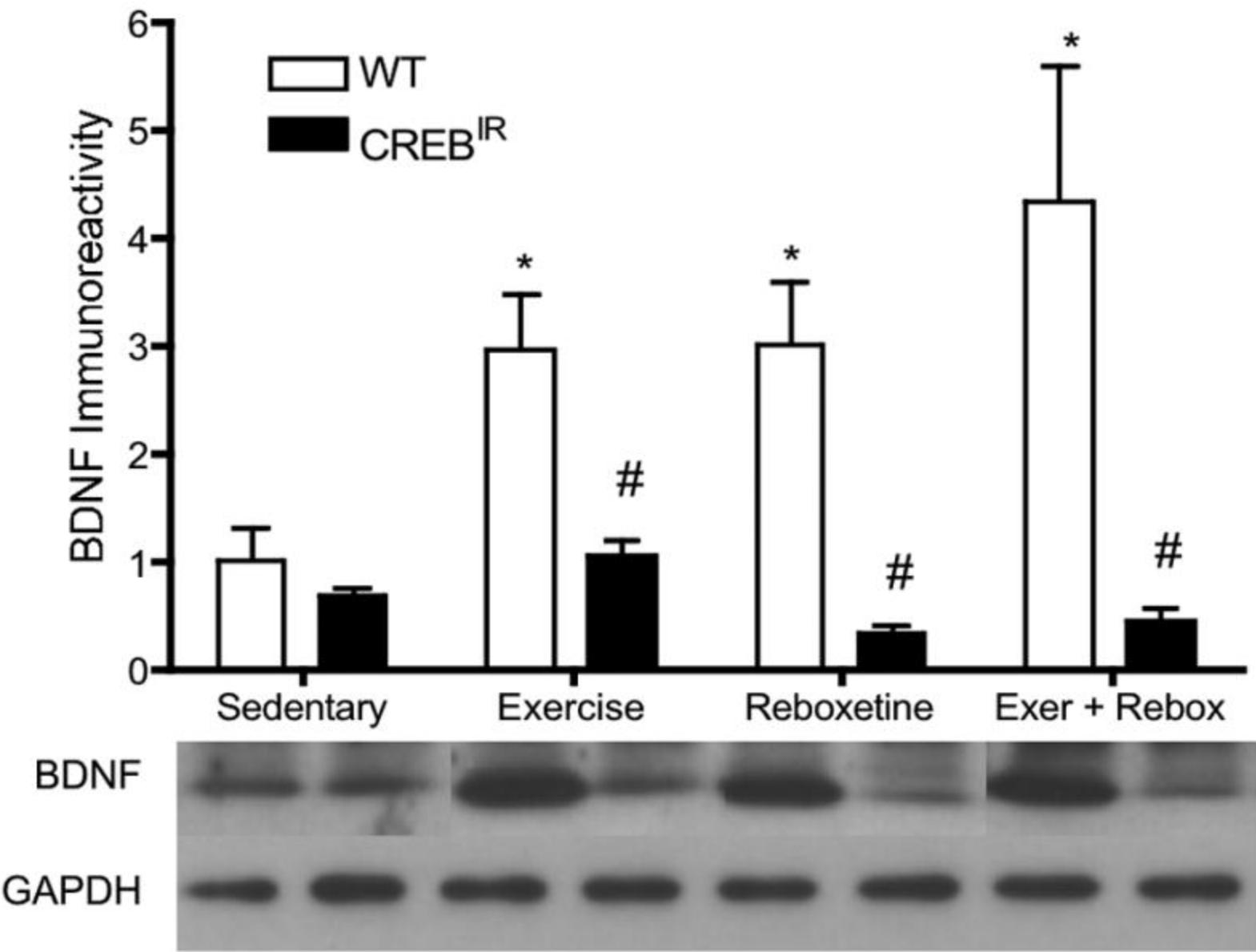


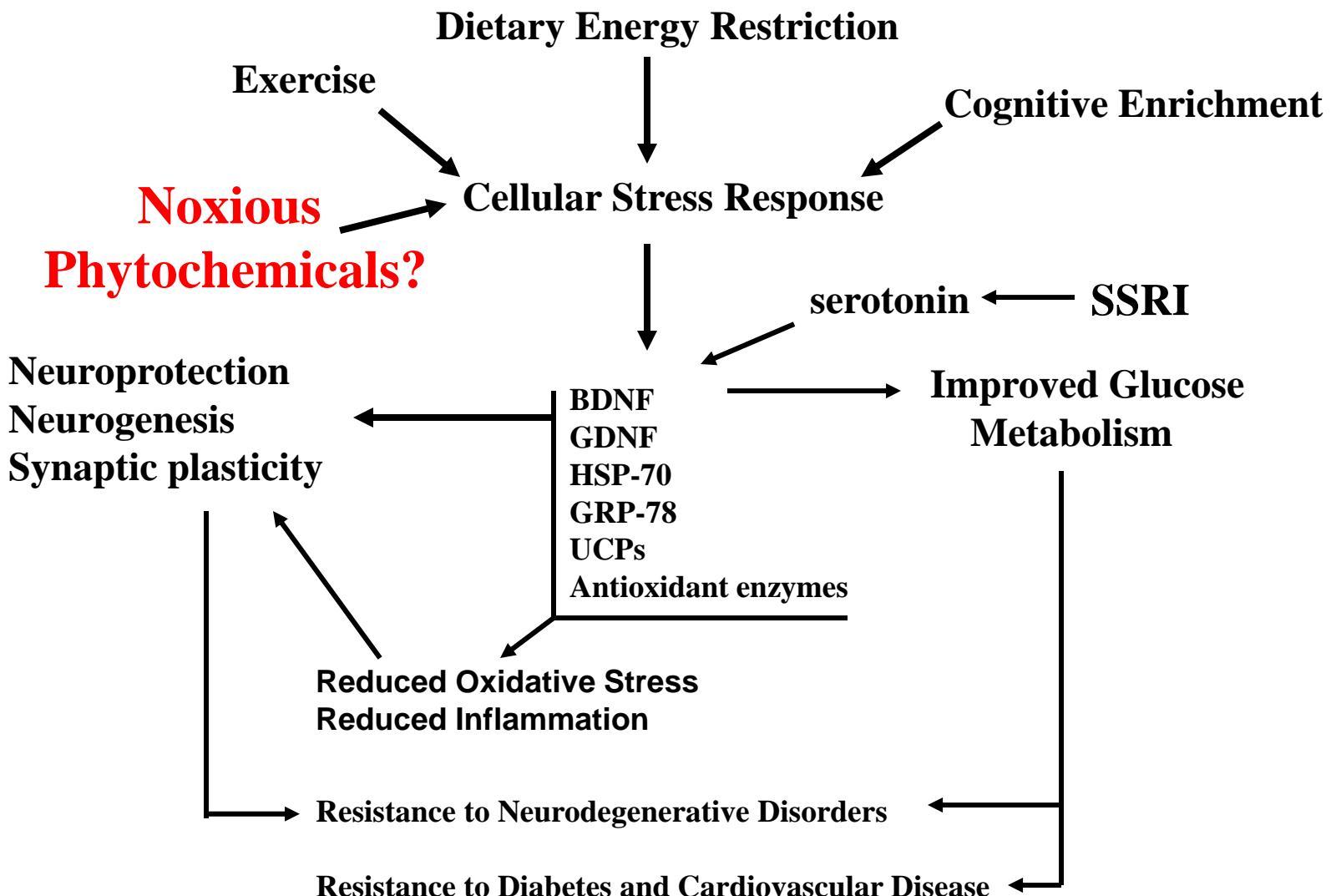
Conclusions: Excitatory activity in nerve cells results in calcium- and mitochondria-mediated oxidative DNA damage which is repaired rapidly as a result of calcium- and CREB-mediated induction of the expression of the BER enzyme APE1. Neuronal activity engages an adaptive stress response that enhances the ability of the neurons to protect their genome against oxidative damage.



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.







Oxidants, antioxidants, and the degenerative diseases of aging

(cancer/mutation/endogenous DNA adducts/oxygen radicals)

Bruce N. Ames*, Mark K. Shigenaga, and Tory M. Hagen

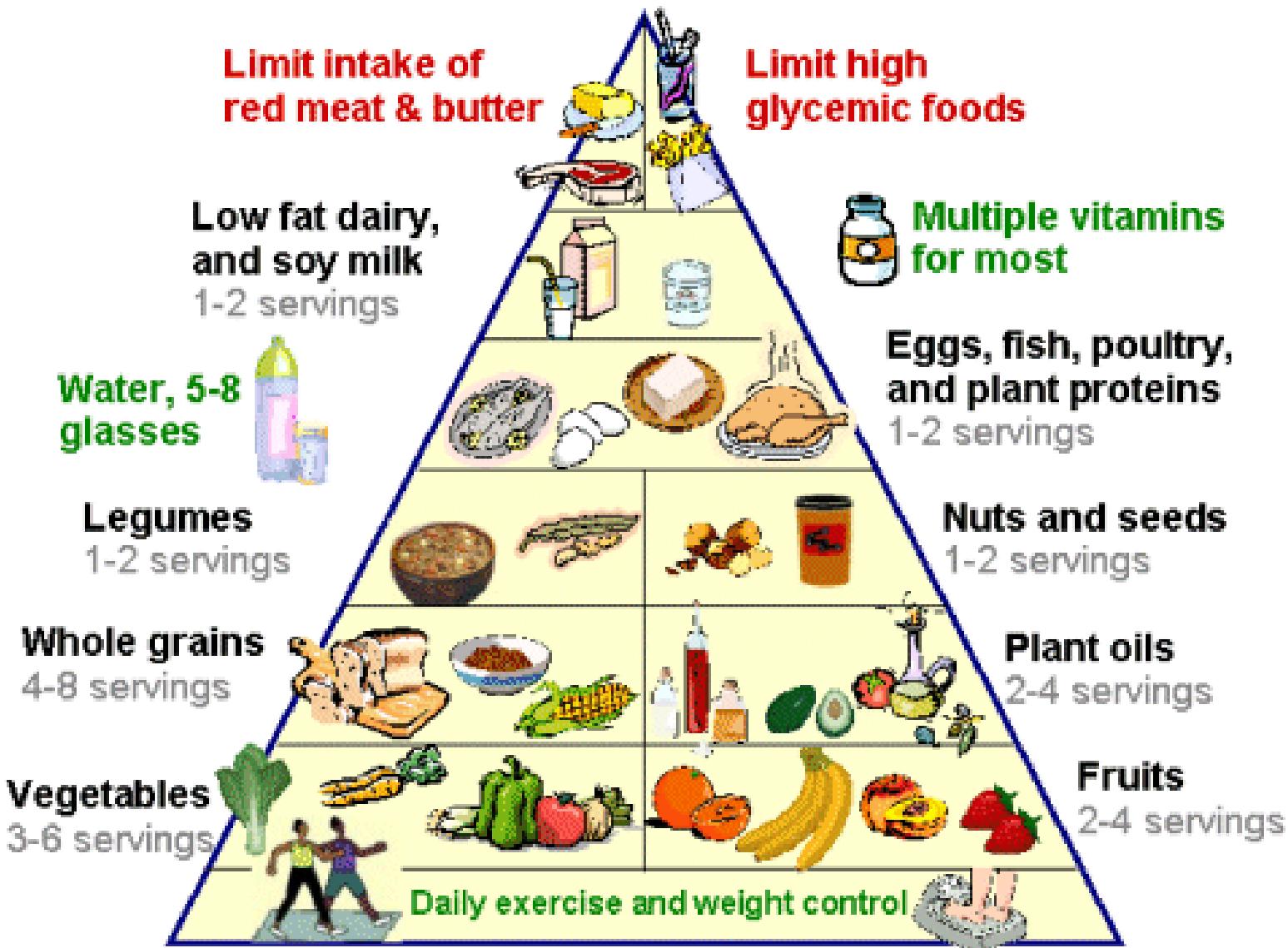
Division of Biochemistry and Molecular Biology, University of California, Berkeley, CA 94720

Table 1. Review of epidemiological studies by Block *et al.* (93) showing protection by fruits and vegetables against cancer

| Cancer site | Fraction of studies showing protection | Relative risk (median) |
|--------------------------|--|------------------------|
| Epithelial | | |
| Lung | 24/25 | 2.2 |
| Oral | 9/9 | 2.0 |
| Larynx | 4/4 | 2.3 |
| Esophagus | 15/16 | 2.0 |
| Stomach | 17/19 | 2.5 |
| Pancreas | 9/11 | 2.8 |
| Cervix | 7/8 | 2.0 |
| Bladder | 3/5 | 2.1 |
| Colorectal | 20/35 | 1.9 |
| Miscellaneous | 6/8 | — |
| Hormone-dependent | | |
| Breast | 8/14 | 1.3 |
| Ovary/endometrium | 3/4 | 1.8 |
| Prostate | 4/14 | 1.3 |
| Total | 129/172 | |

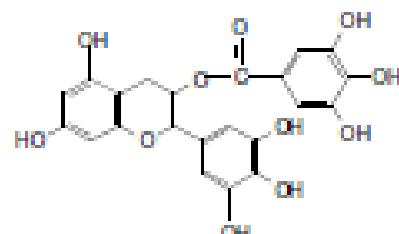
ABSTRACT Metabolism, like other aspects of life, involves tradeoffs. Oxidant by-products of normal metabolism cause extensive damage to DNA, protein, and lipid. We argue that this damage (the same as that produced by radiation) is a major contributor to aging and to degenerative diseases of aging such as cancer, cardiovascular disease, immune-system decline, brain dysfunction, and cataracts. Antioxidant defenses against this damage include ascorbate, tocopherol, and carotenoids. Dietary fruits and vegetables are the principal source of ascorbate and carotenoids and are one source of tocopherol. Low dietary intake of fruits and vegetables doubles the risk of most types of cancer as compared to high intake and also markedly increases the risk of heart disease and cataracts. Since only 9% of Americans eat the recommended five servings of fruits and vegetables per day, the opportunity for improving health by improving diet is great.

New Food Pyramid

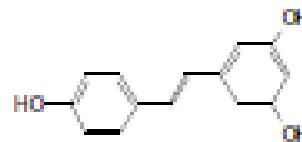




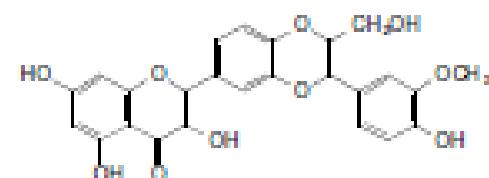
Humans evolved from species that were primarily herbivores.
Therefore our cells developed adaptive responses to potentially toxic phytochemicals



(-) -Epigallocatechin-3-gallate



Resveratrol



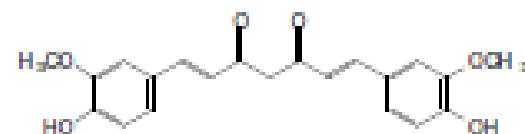
Silybin



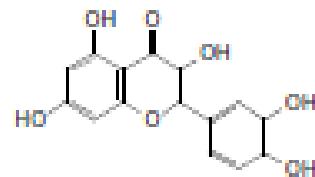
Sulforaphane



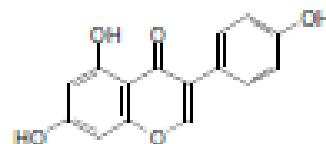
Phenethyl isothiocyanate



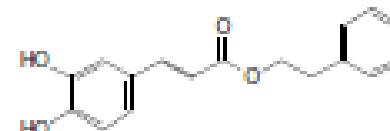
Curcumin



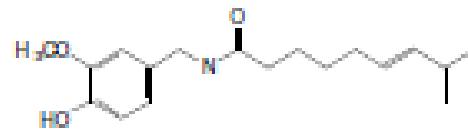
Quercetin



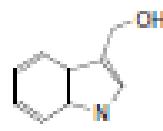
Genistein



Caffeic acid phenethyl ester



Capsaicin



Indole-3-carbinol



Diallyl trisulfide

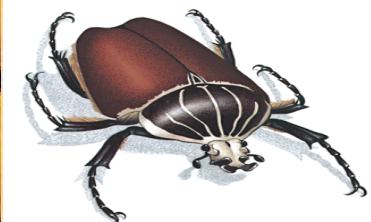
Resveratrol



Sulforaphane



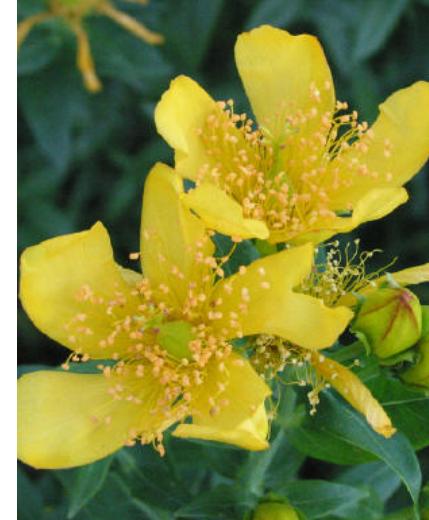
Curcumin



Catechins



Allicin



Hypericin

Mattson MP, Cheng A (2006) Neurohormetic phytochemicals: Low-dose toxins that induce adaptive neuronal stress responses. *Trends Neurosci.* 29:632-639.

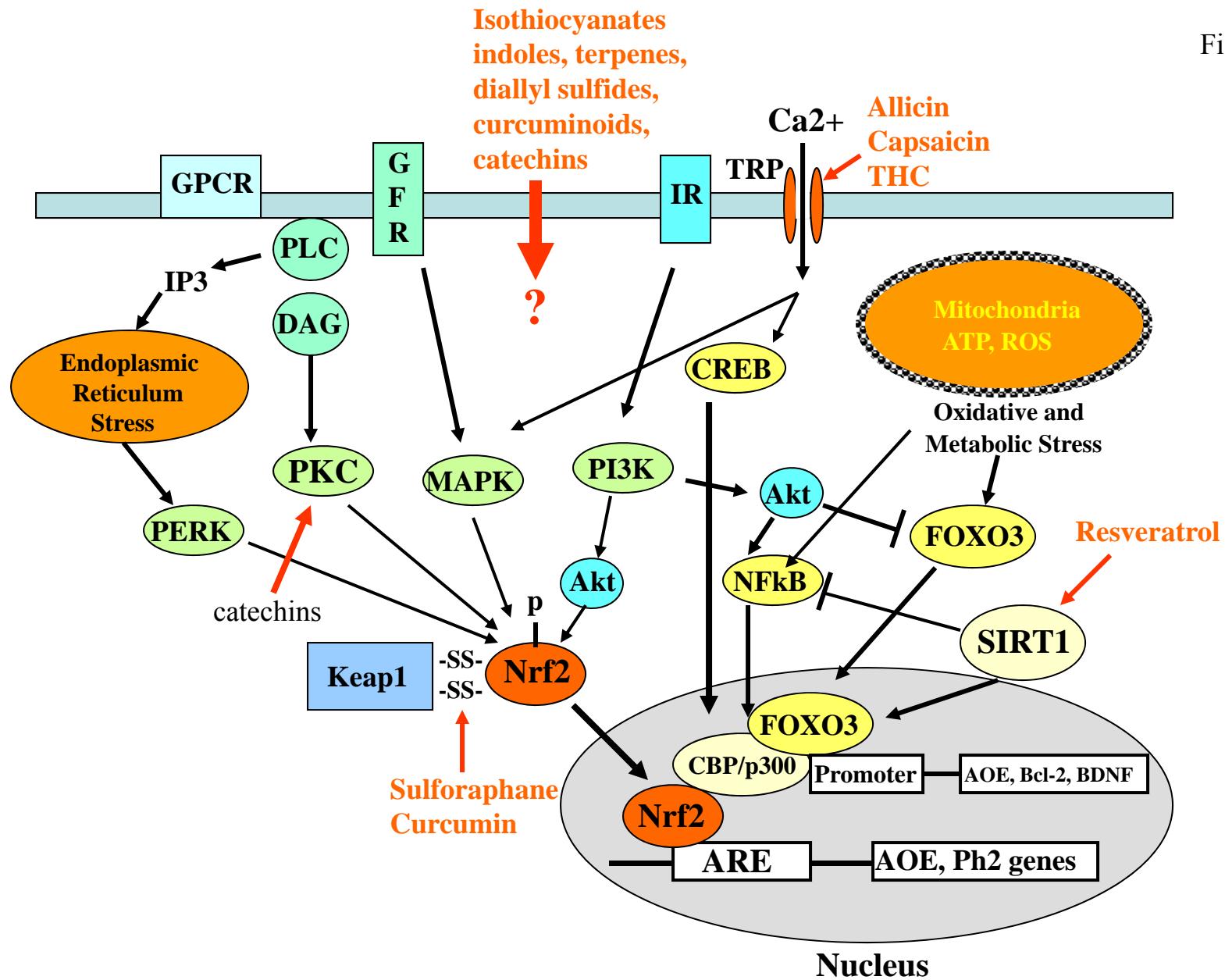
INSECT ANTIFEEDANTS

Opender Koul



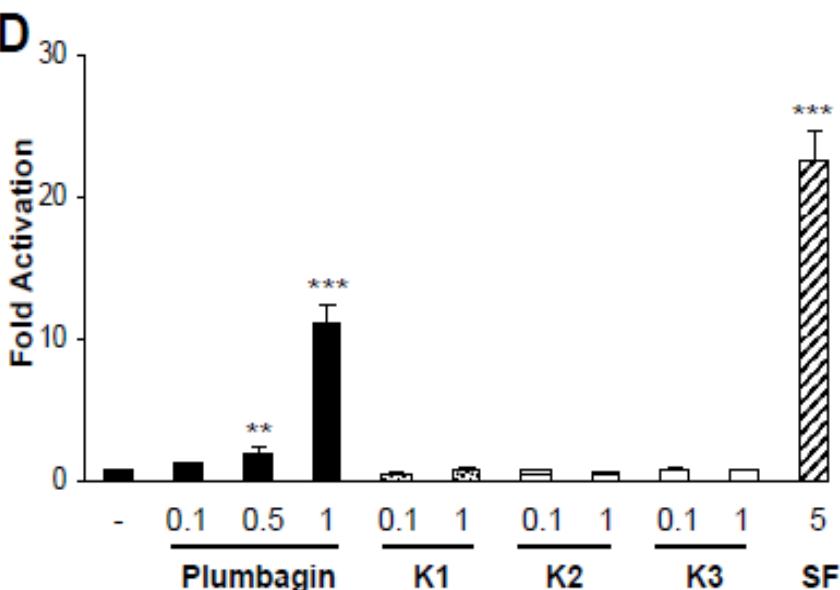
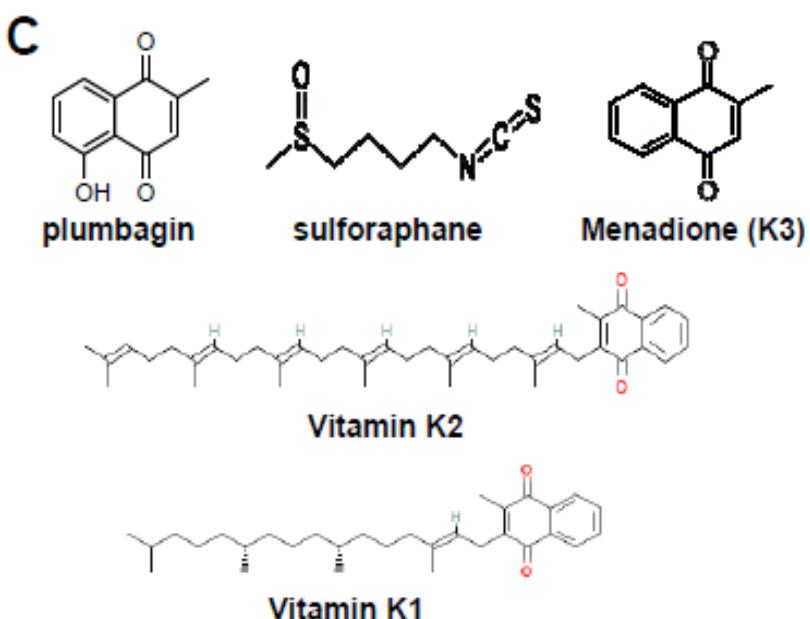
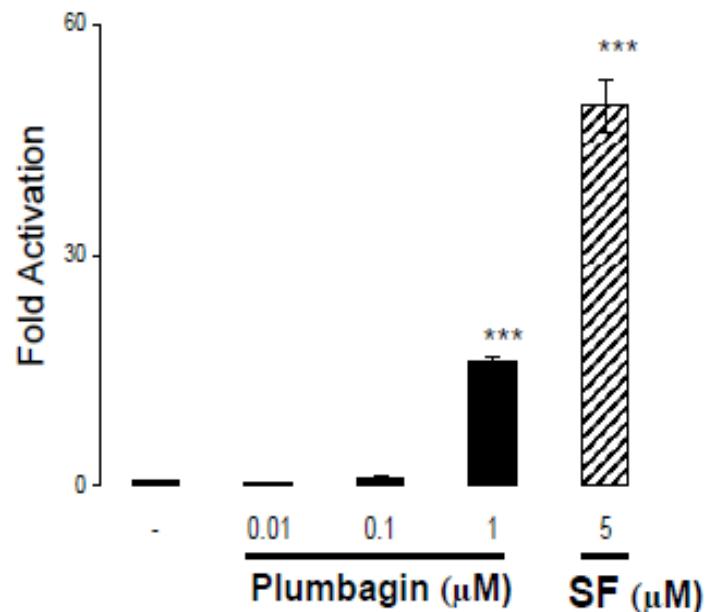
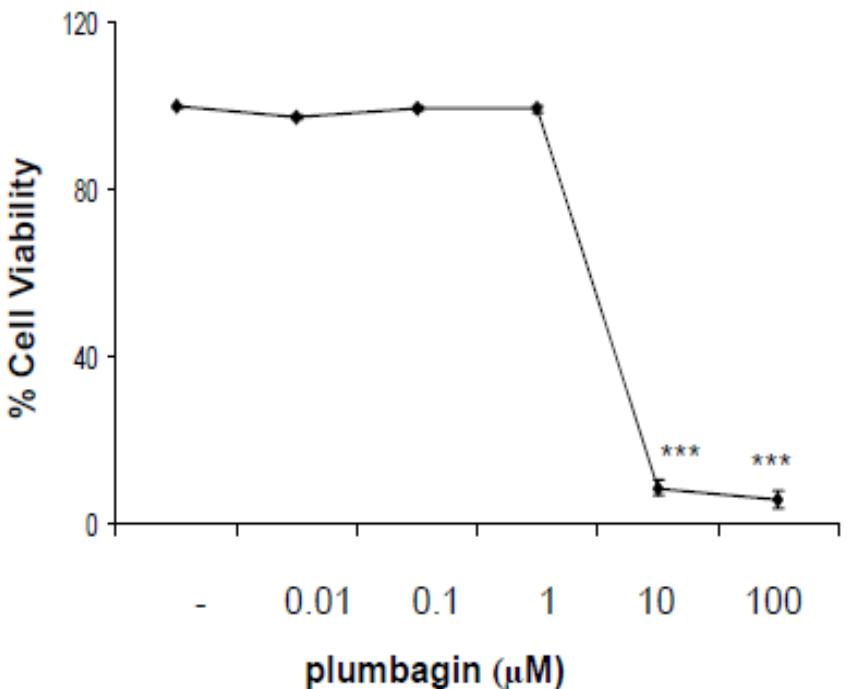
“Most plant defense mechanisms discourage herbivory by deterring feeding and oviposition or by impairing larval growth rather than killing the insect.“

Figure 3

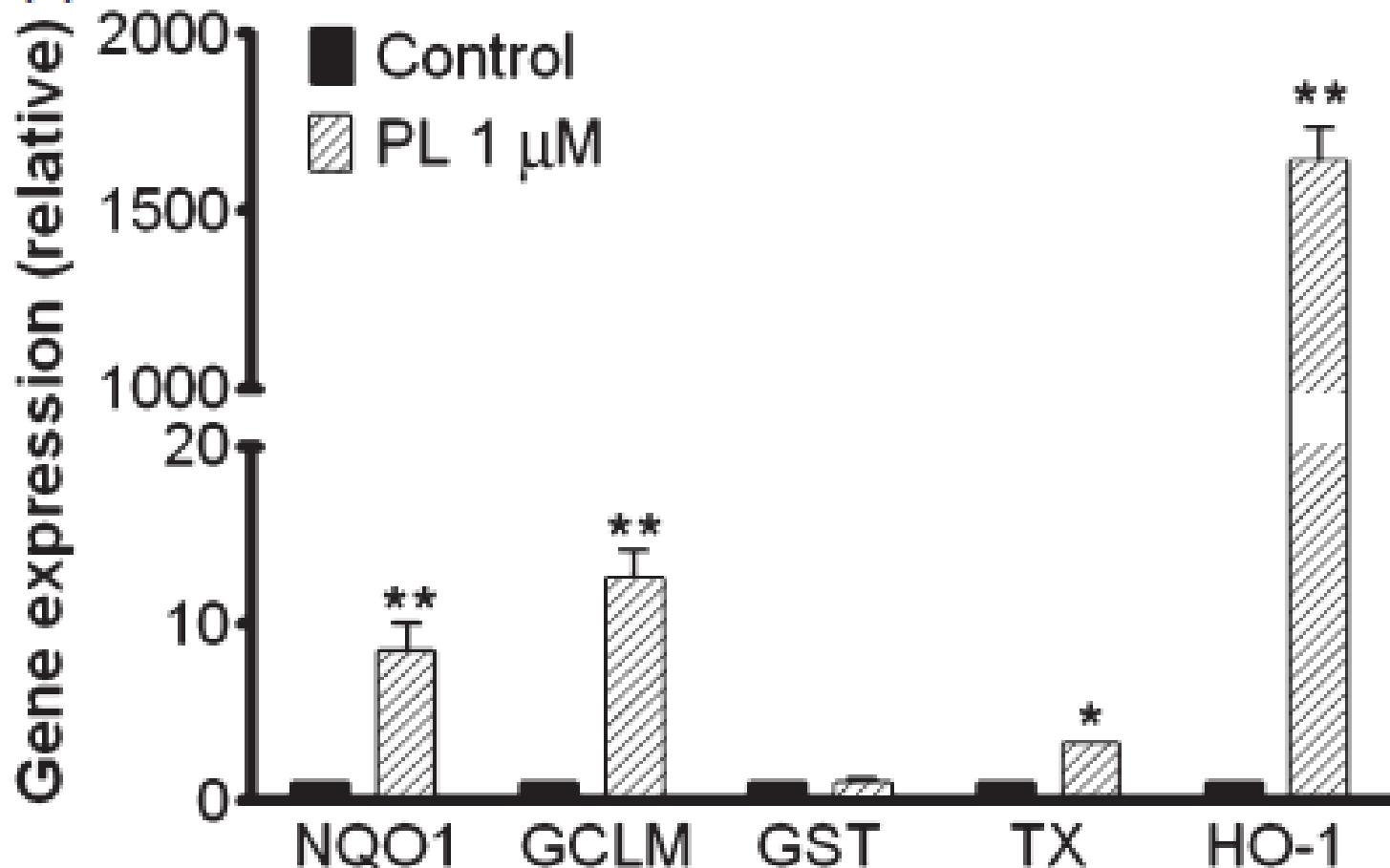


| | Compound Name | Gene Induction (fold increase) | | |
|----|--|--------------------------------|------|------|
| | | ARE | FOXO | NFkB |
| | | - | - | - |
| 1 | Piperine (PP) | - | 2.7 | - |
| 2 | Visnagin (Vis) | - | - | - |
| 3 | Veratrine (V) | - | - | - |
| 4 | L-canavanine (JB) | - | - | - |
| 5 | Trans-2,4,5-trimethoxy propenylbenene (R2) | - | - | - |
| 6 | Precocene (PC) | - | - | - |
| 7 | Anabasine (AM) | - | - | - |
| 8 | Eugenol (EG) | - | - | - |
| 9 | Apiole (AP) | - | - | - |
| 10 | Aristolochic acid (A) | - | - | - |
| 11 | Resveratrol (RV) | - | 3.8 | - |
| 12 | 5-Hydroxy-1,4-naphthaquinone (HN) | - | - | - |
| 13 | Sesamin (SE) | - | - | - |
| 14 | Plumbagin (P) | 15 | - | 2 |
| 15 | tert-butylhydroquinone (BHQ) | - | - | - |
| 16 | Farnesol (F) | - | - | - |
| 17 | Sulforaphane (SF) | 27 | - | - |
| 18 | Flavone (FL) | - | - | 4.5 |
| 19 | Silymarin (Sil) | - | 2.4 | 5 |
| 20 | Indole (IN) | - | - | - |
| 21 | N,N-Diethyl-m-toluamide (DEET) | - | - | 4.7 |
| 22 | phylloquinone (vitamin K1) | - | - | - |
| 23 | Menaquinone (vitamin K2) | - | - | - |
| 24 | Menadione (vitamin K3) | - | - | - |

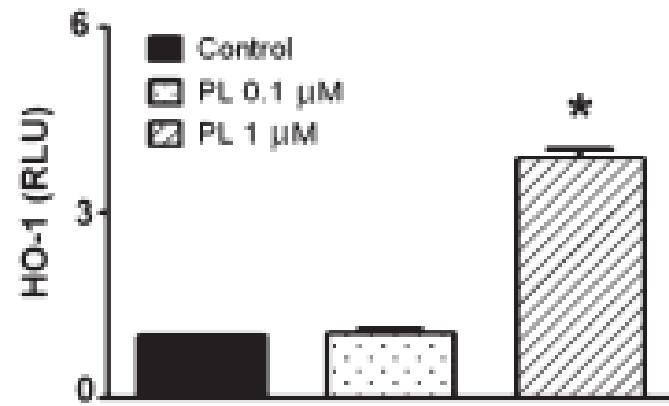
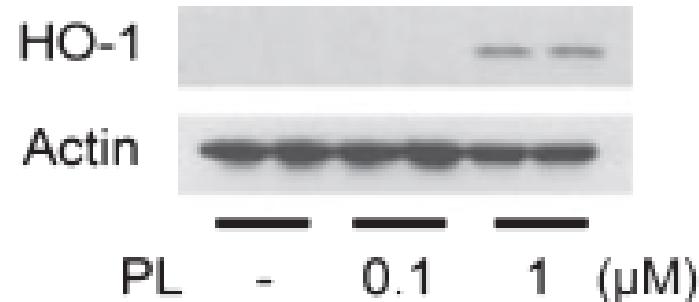




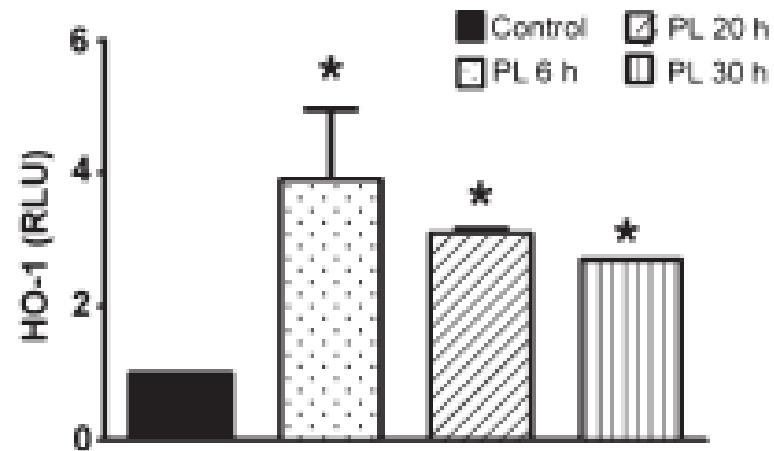
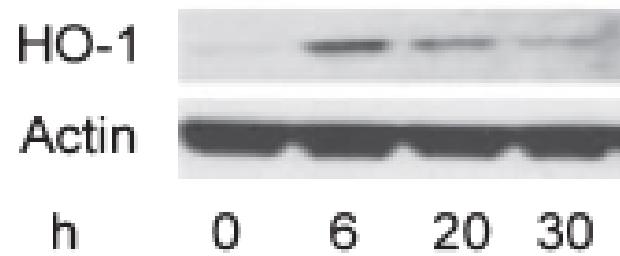
(a)

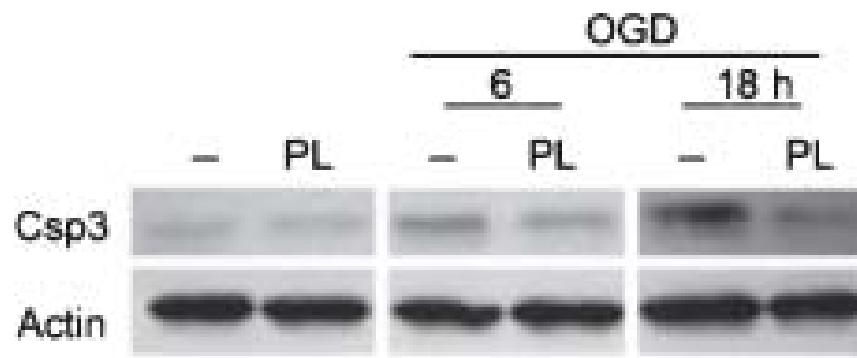
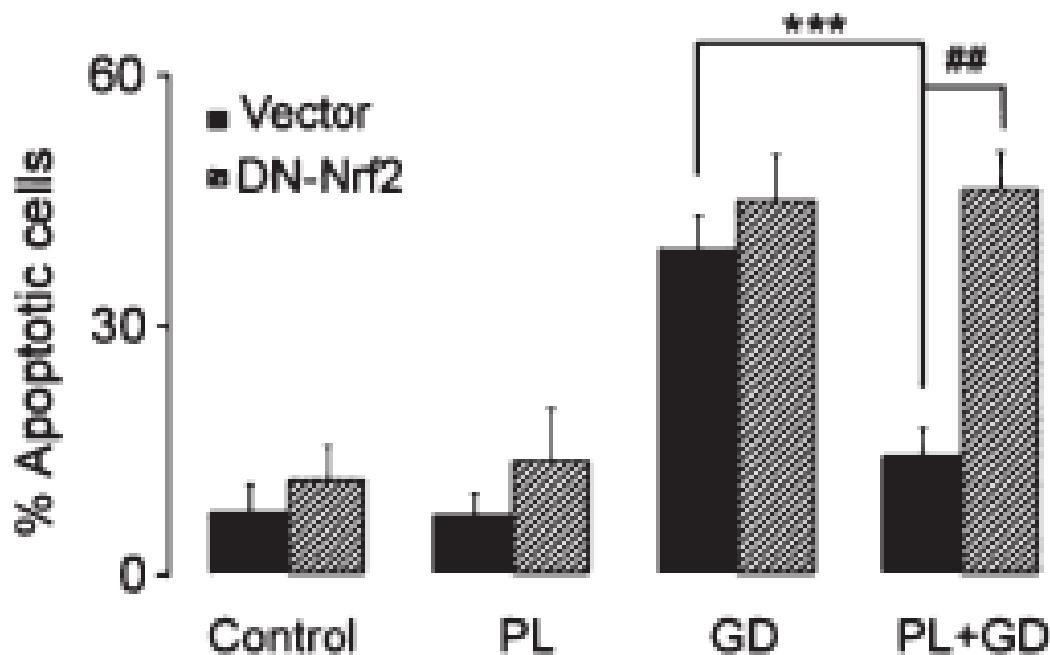


(b)



(c)





H0-1



Cortex

Tubulin



H0-1



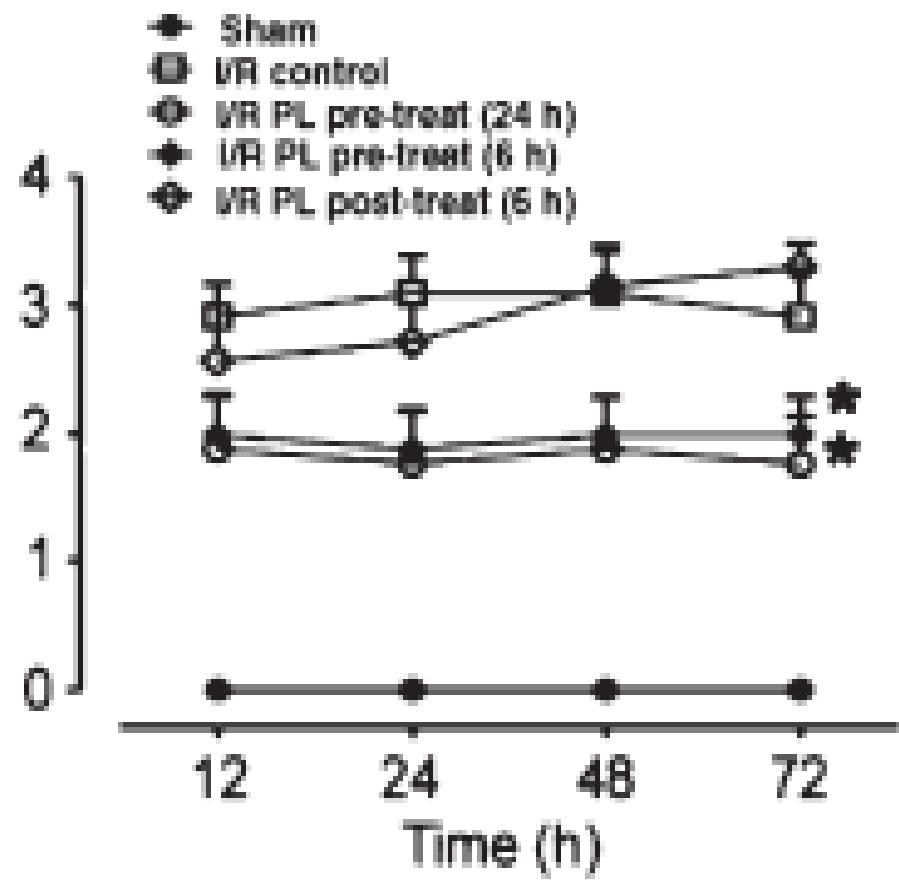
Striatum

Tubulin

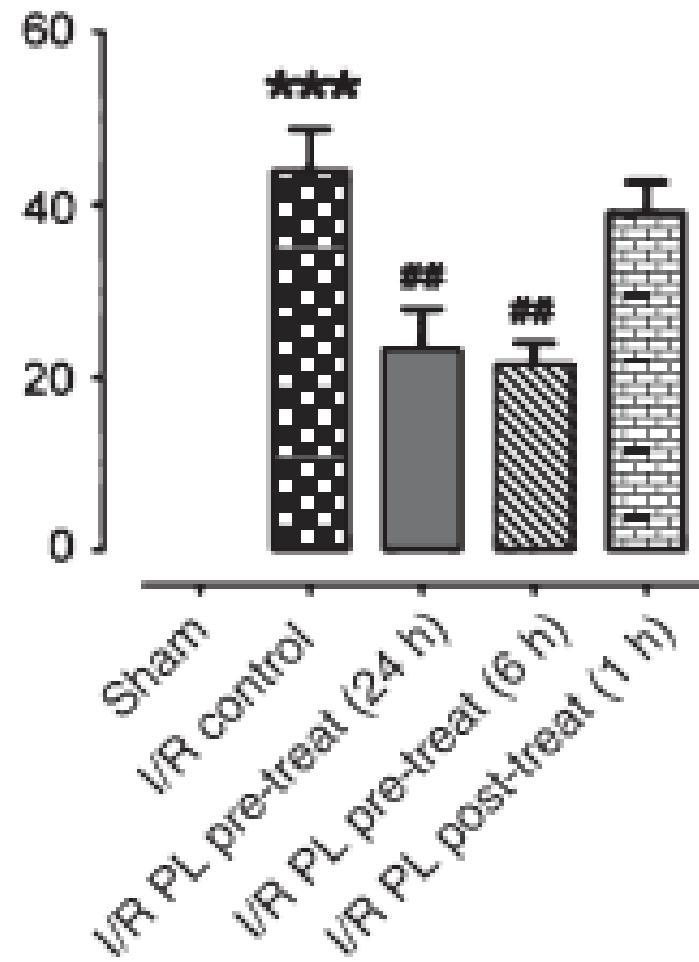


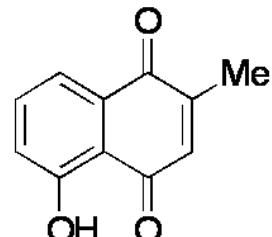
- 6 24 - 6 24 6 24 (h)

Neurological deficit score

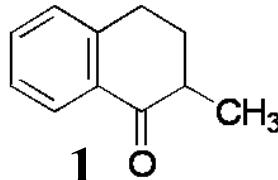


Ipsilateral infarct volume (%)

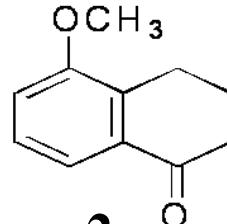




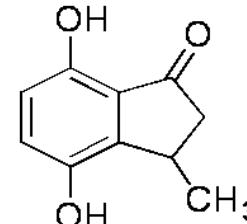
plumbagin



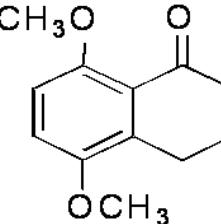
1



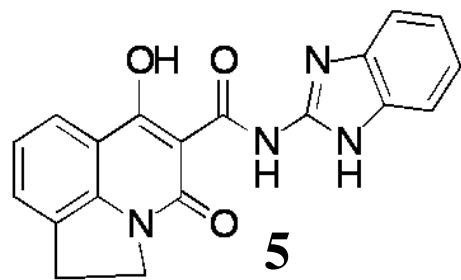
2



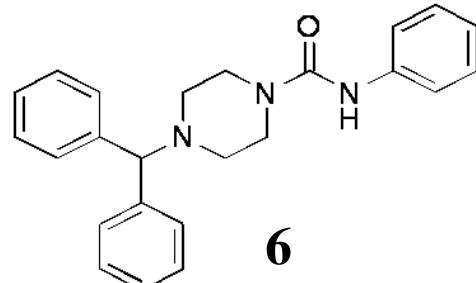
3



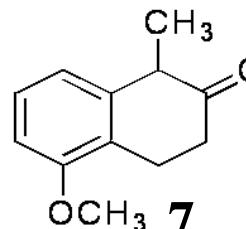
4



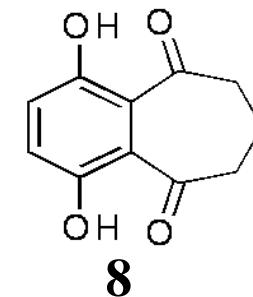
5



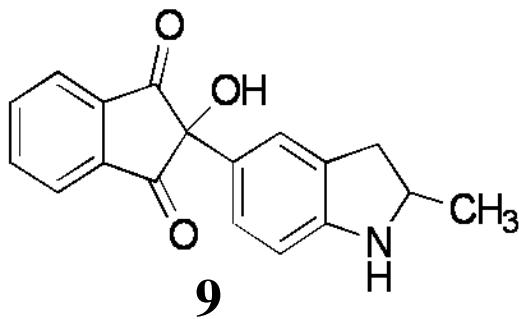
6



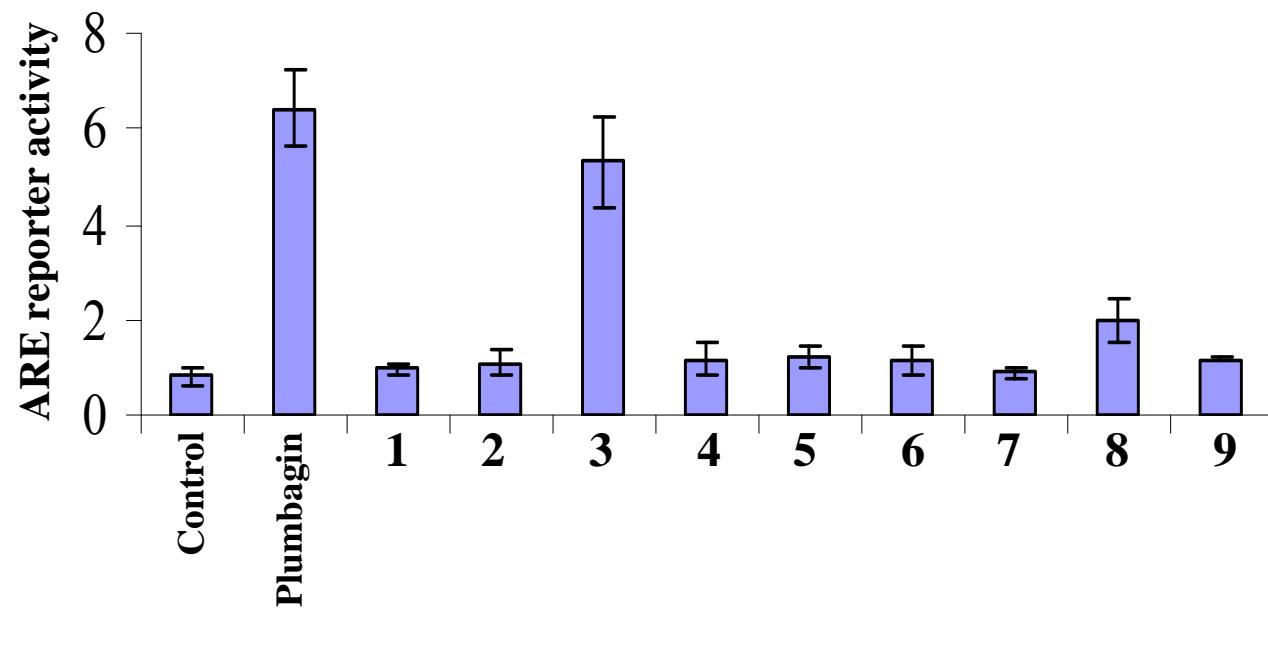
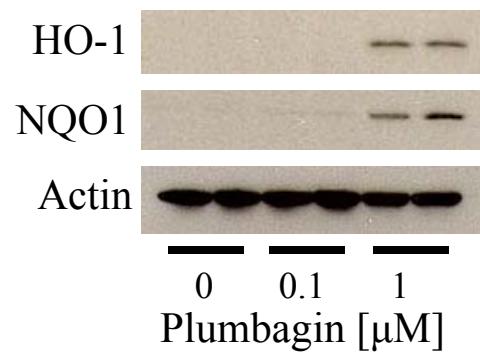
7



8



9



Lab Members

Dong Liu
Roy Cutler
Peisu Zhang
Ruiqian Wan
Pamela Yao

Yonquan Luo

Mohamed Mughal

Emmette Hutchison
Kathy Griffioen
Aiwu Cheng

Yan Hou

Elisa Kawamoto
Yue Wang

Marc Gleichmann
Simonetta Camandola

Jeong Yoon
Eitan Okun
Catherine Schwartz
Sarah Rothman
Jenq-Lin Yang
Sarah Texel

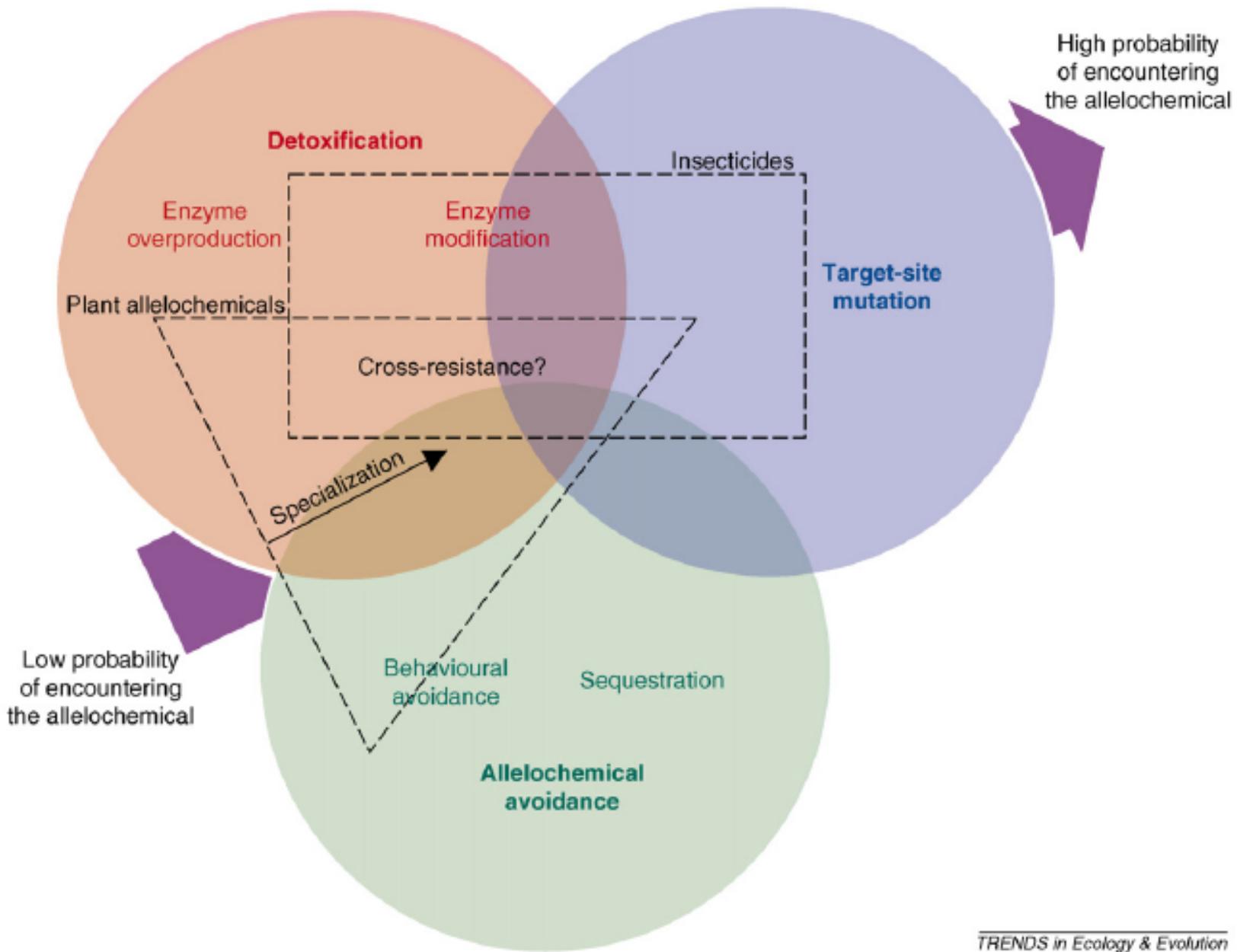
Former Lab Members

Steve Barger
Anna Bruce-Keller
Katsutoshi Furukawa
Qing Guo
Carsten Culmsee
Sung-Chun Tang
Marc Gleichmann

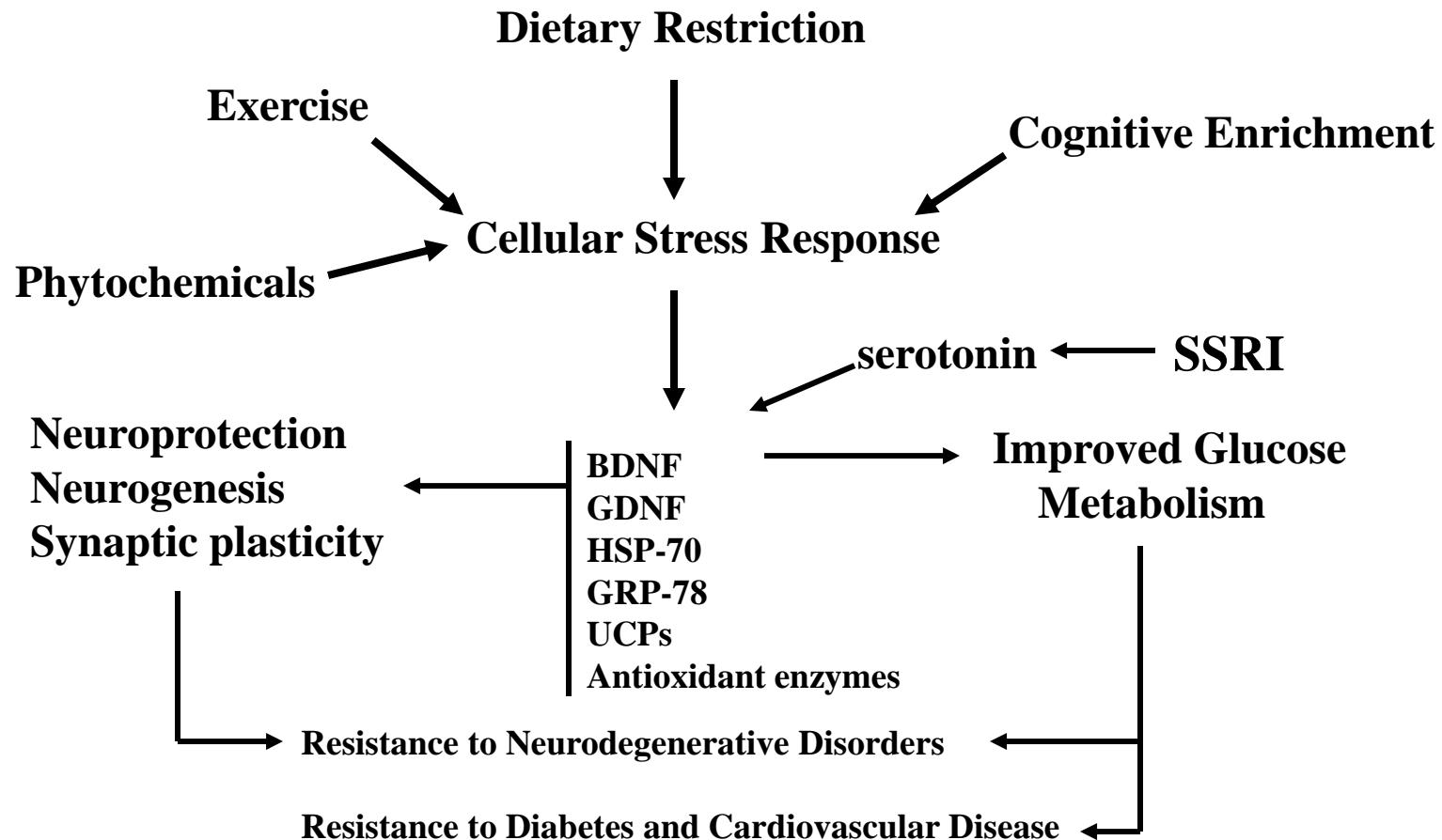
Bronwen Martin

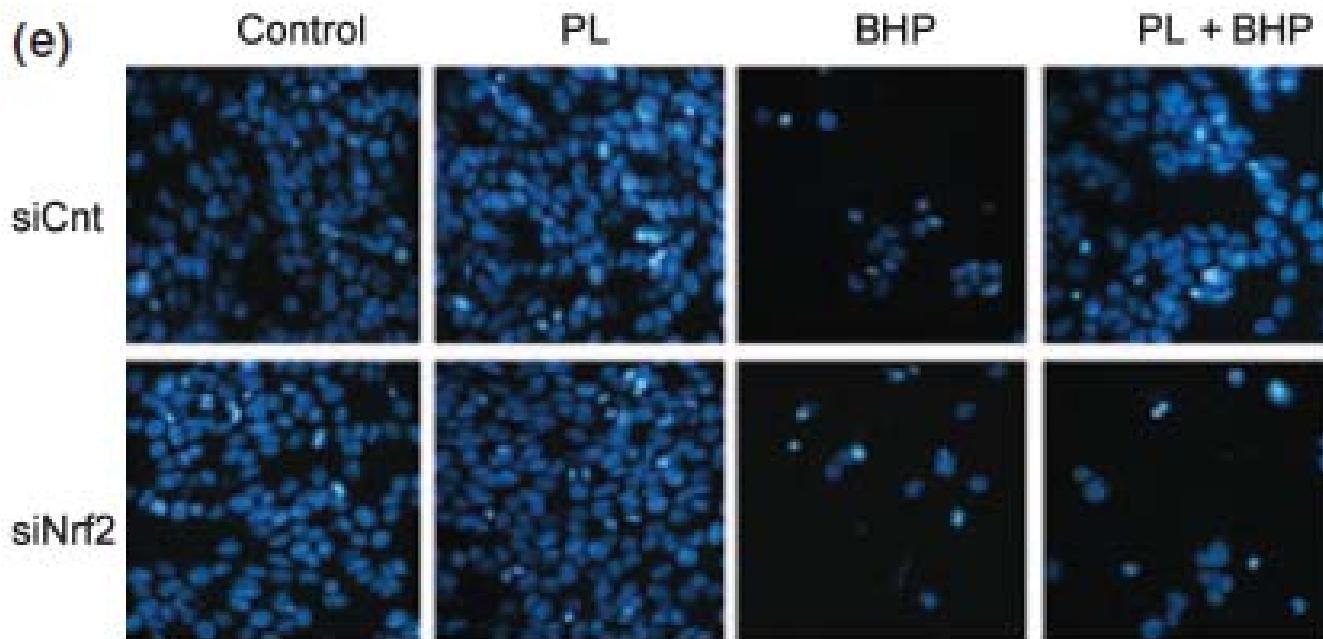
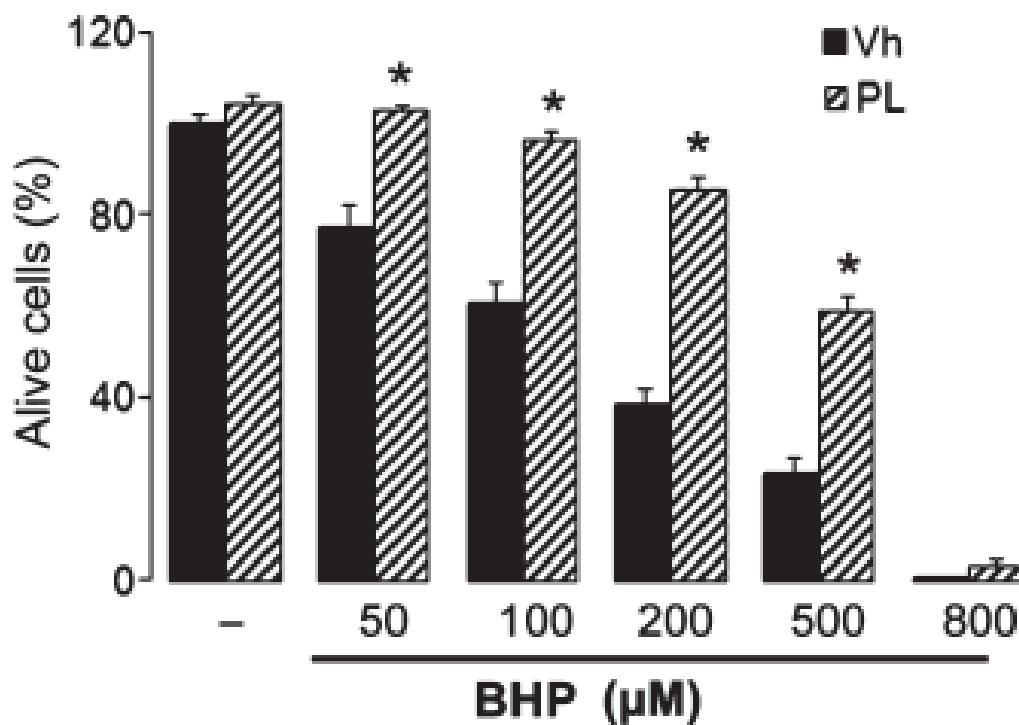
Bob Mark
Jeff Keller
Norm Haughey
Veerendra Halagappa
Wenzhen Duan
Jaewon Lee
Devin Gary
Olivier Milhavet
Justin Lathia
Inna Kruuman
Alexis Stranahan

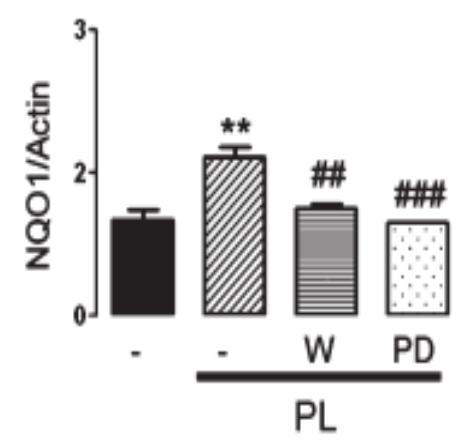
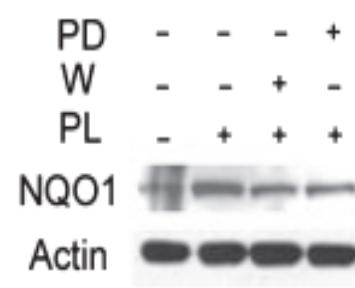
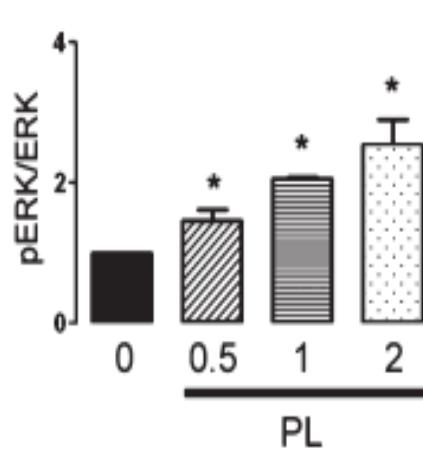
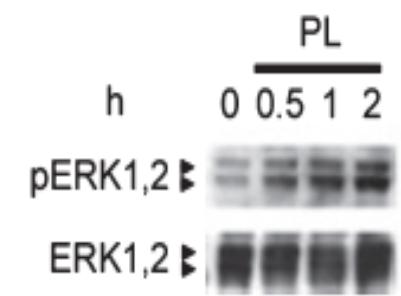
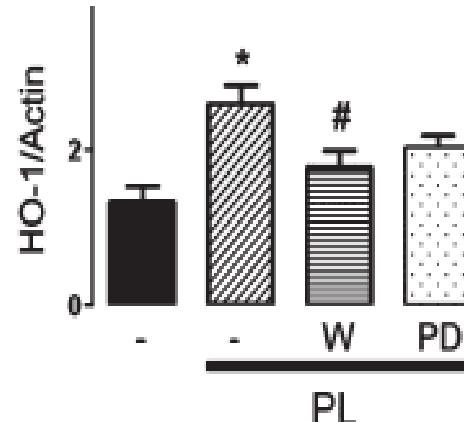
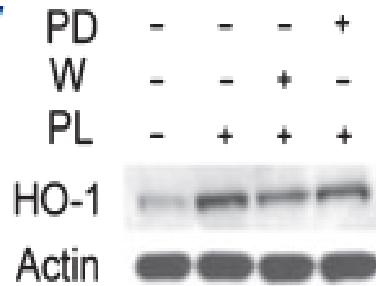
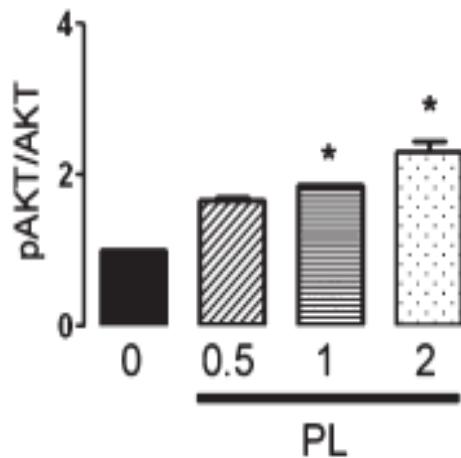
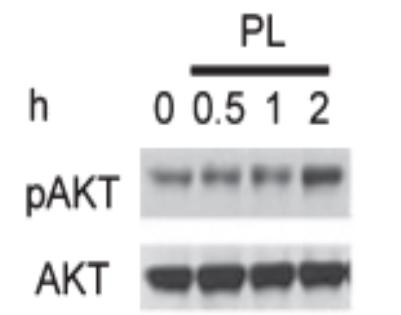
Navin Maswood
Sic (Stephen) Chan
Garrie Arumugam
Tae Gen Son
Tim Magnus
Dong-Gyu Jo



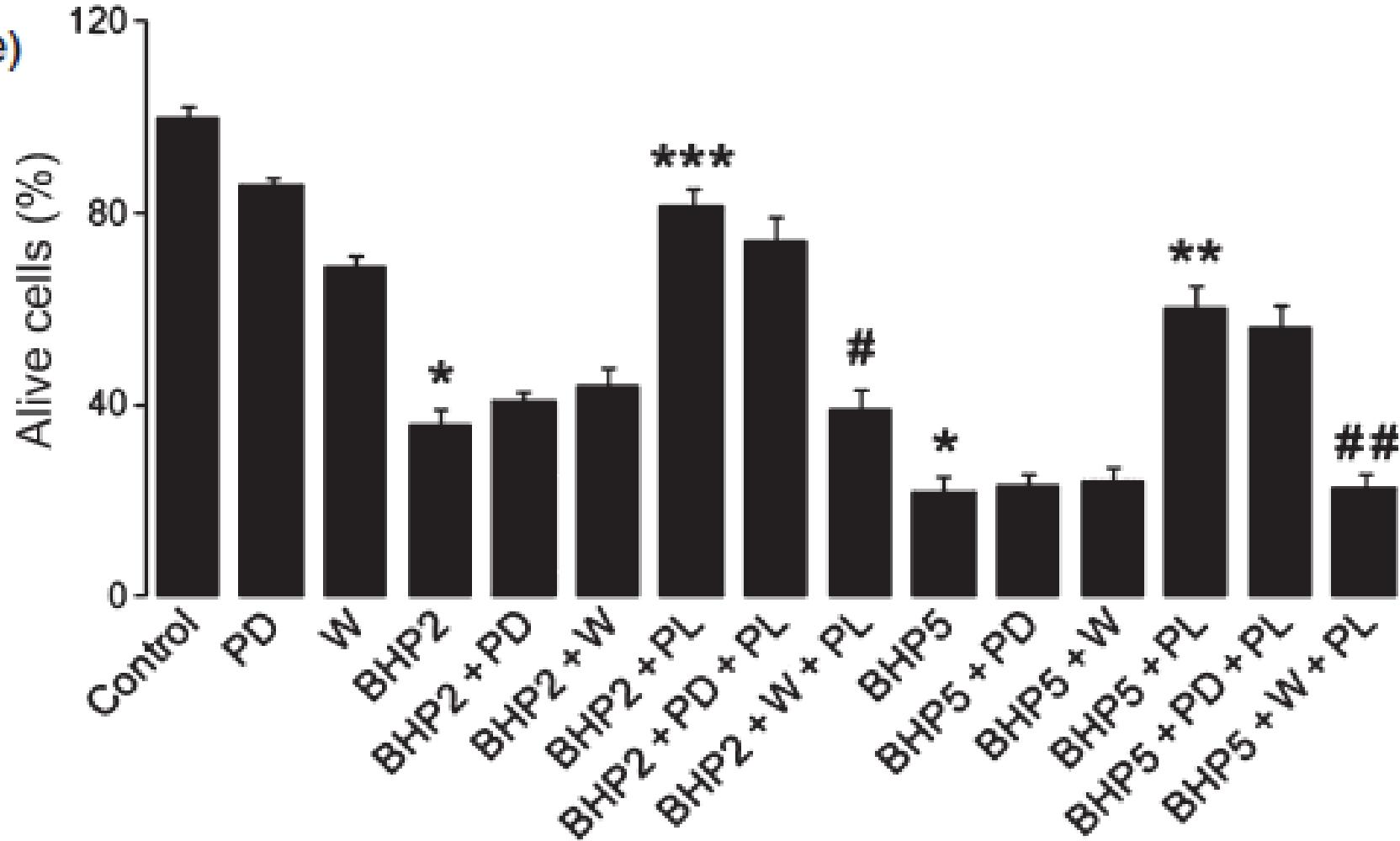
Dietary and Behavioral Neurohormesis

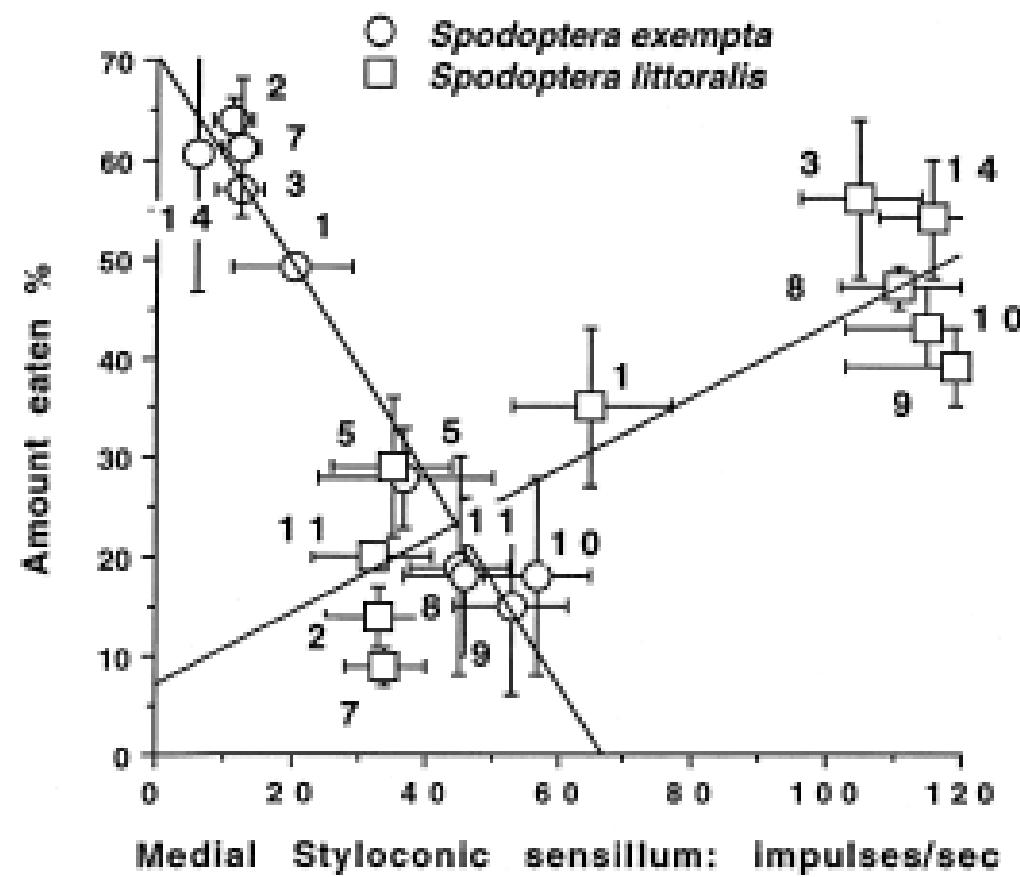
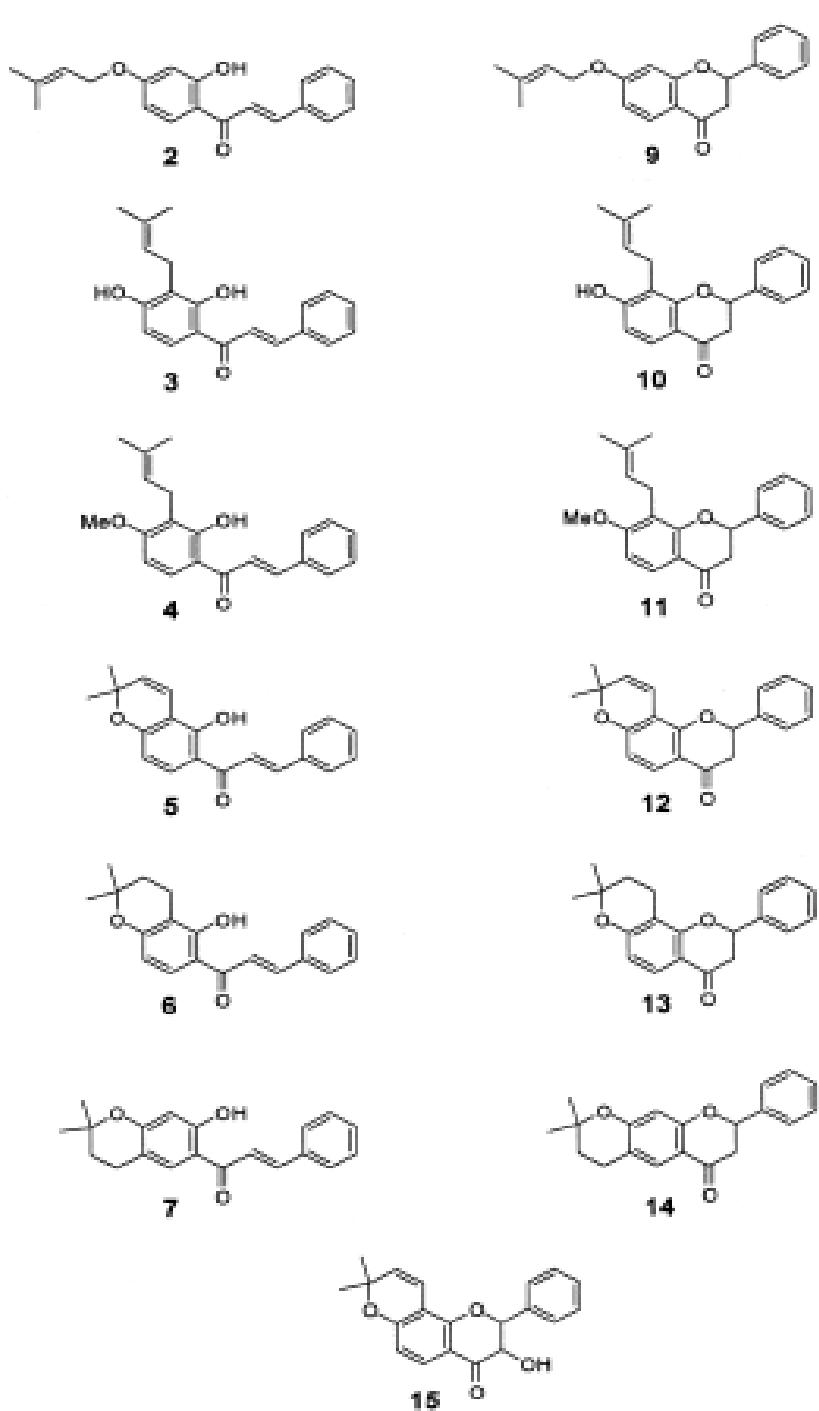






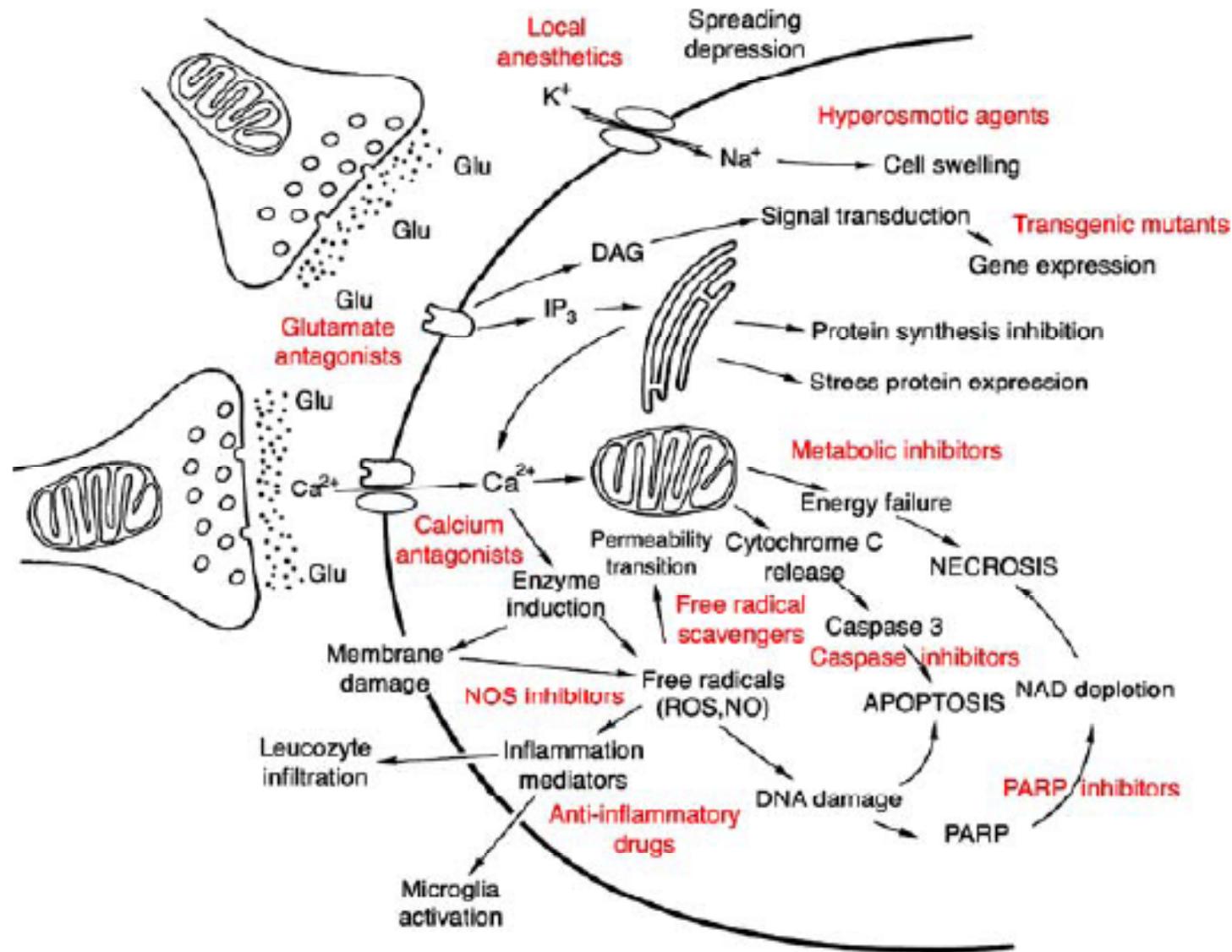
(e)





Importance of flavonoids in insect–plant interactions:
feeding and oviposition

Monique S.J. Simmonds *



Hossmann, 2006

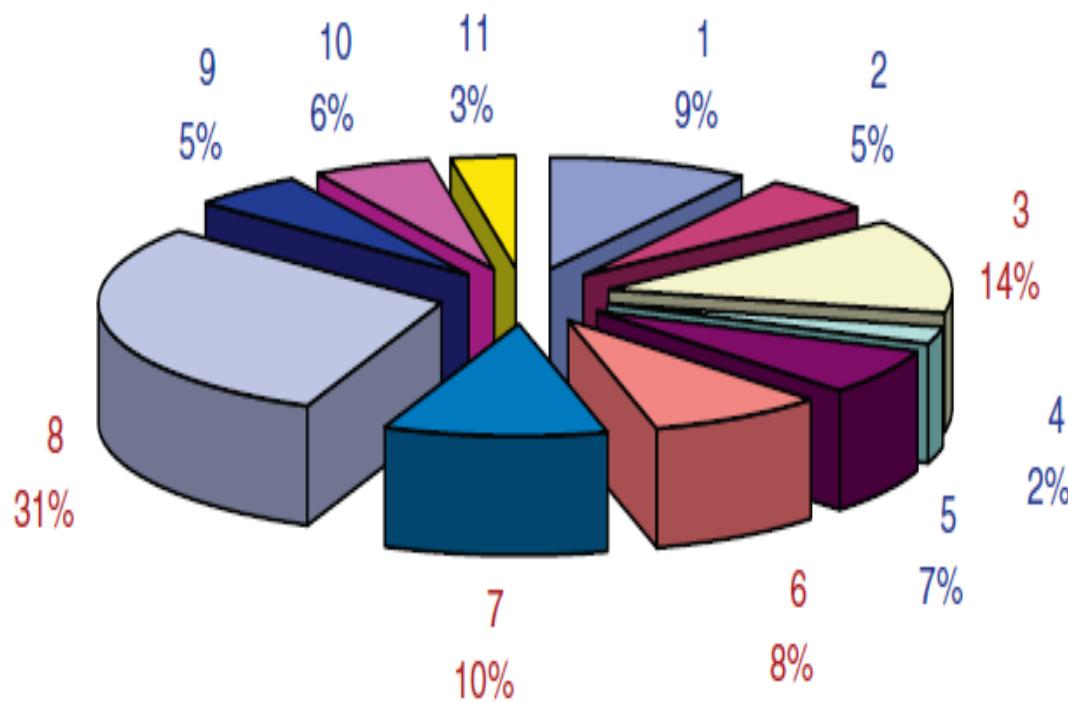
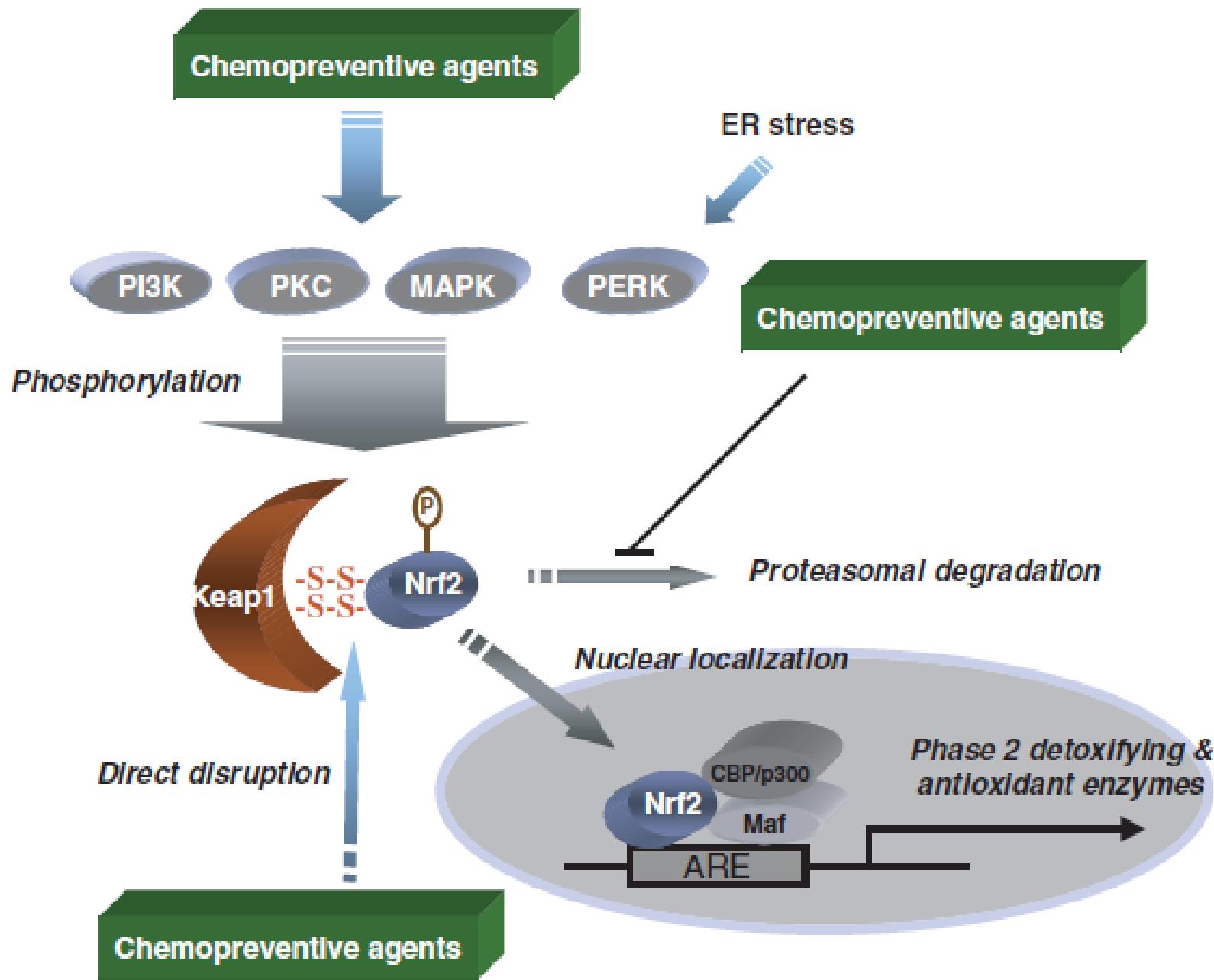
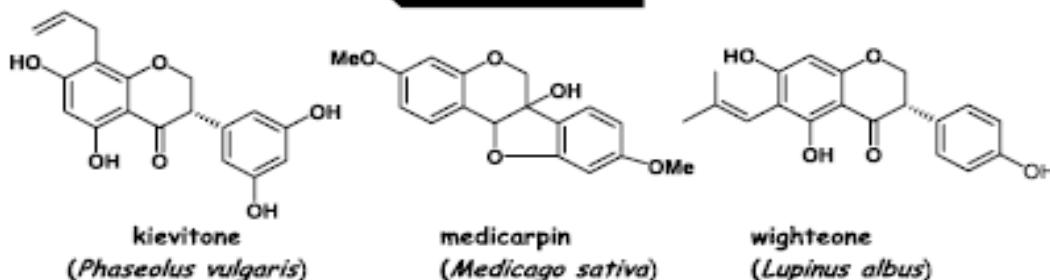


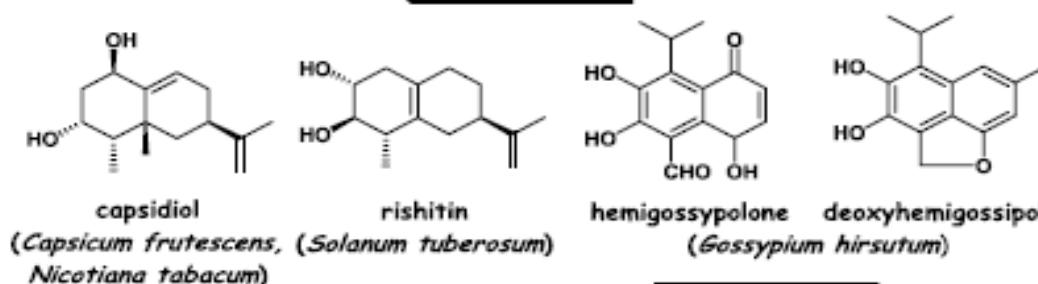
Fig. 9. Classification of allelopathic agents and relative abundance according to results published until year 2001. Key: 1: simple aliphatic compounds; 2: fatty acids and polyacetylenes; 3: benzoic and cinnamic acids; 4: quinines; 5: coumarins; 6: flavonoids; 7: monoterpenes; 8: sesquiterpenes; 9: other terpenoids; 10: nitrogen-containing compounds; 11: sulphur-containing compounds. Classes number 3, 6, 7, and 8 account for 63% of total number of compounds, being the most widespread and cited allelopathic agents.



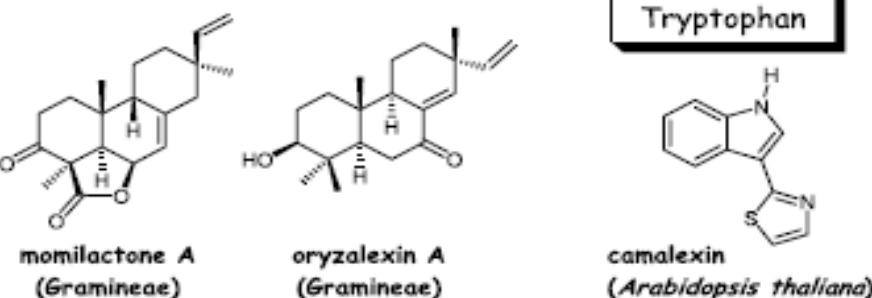
Isoflavones



Terpenoids



Tryptophan



Stilbenes

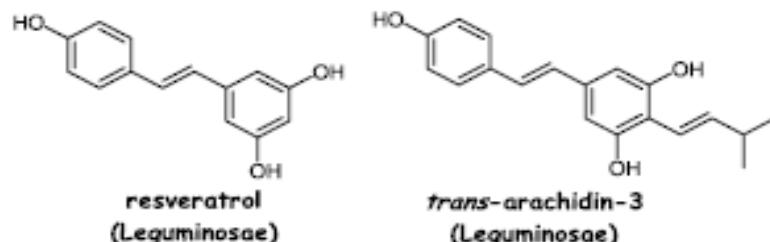


Figure 3

