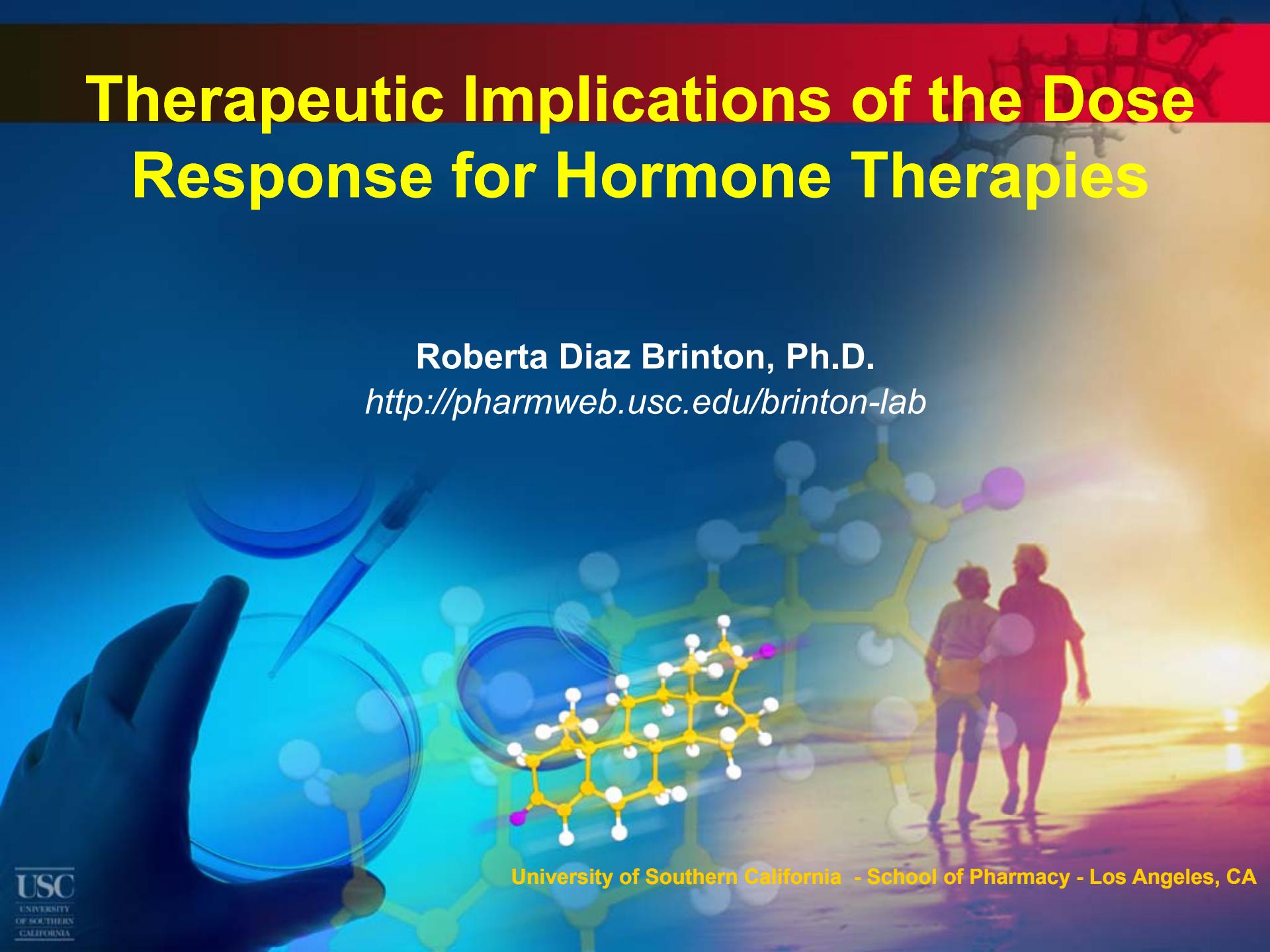


Therapeutic Implications of the Dose Response for Hormone Therapies

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<http://pharmweb.usc.edu/brinton-lab>



University of Southern California - School of Pharmacy - Los Angeles, CA

Alzheimer's Disease: A Women's Health Issue

- 1) 68% of victims of Alzheimer's disease are women.
- 2) Absolute number of women with AD exceeds that of men AND women have a higher incidence of AD relative to age-matched male counterparts
- 3) In 2000 ~ 42 million women > 50 in the United States and of these, > 31 million women were over the age of 55.
- 4) Woman's average life expectancy is ~ 79.7 years.
- 5) A woman who reaches the age of 54 can expect to live to the age of 84.3 years and will spend one-third to one-half of their lifetime in the menopausal state.
- 6) Worldwide, there are currently more than 470 million women aged 50-plus, and 30% of those are projected to live into their 80s.
- 7) Of the 18 million American women in their 70s-80s, 40-50% can be expected to manifest the histopathological changes of Alzheimer's disease.
- 8) Women seek ET/HT for CNS symptom and refuse or discontinue due to fear of breast cancer

Brinton, R.D. *Advances In Neurodegenerative Disorders*, Vol 2:99-144, 1998 Brookmeyer R, Gray S, Kawas C.. Am J Publ 1998; 88: 1337-42

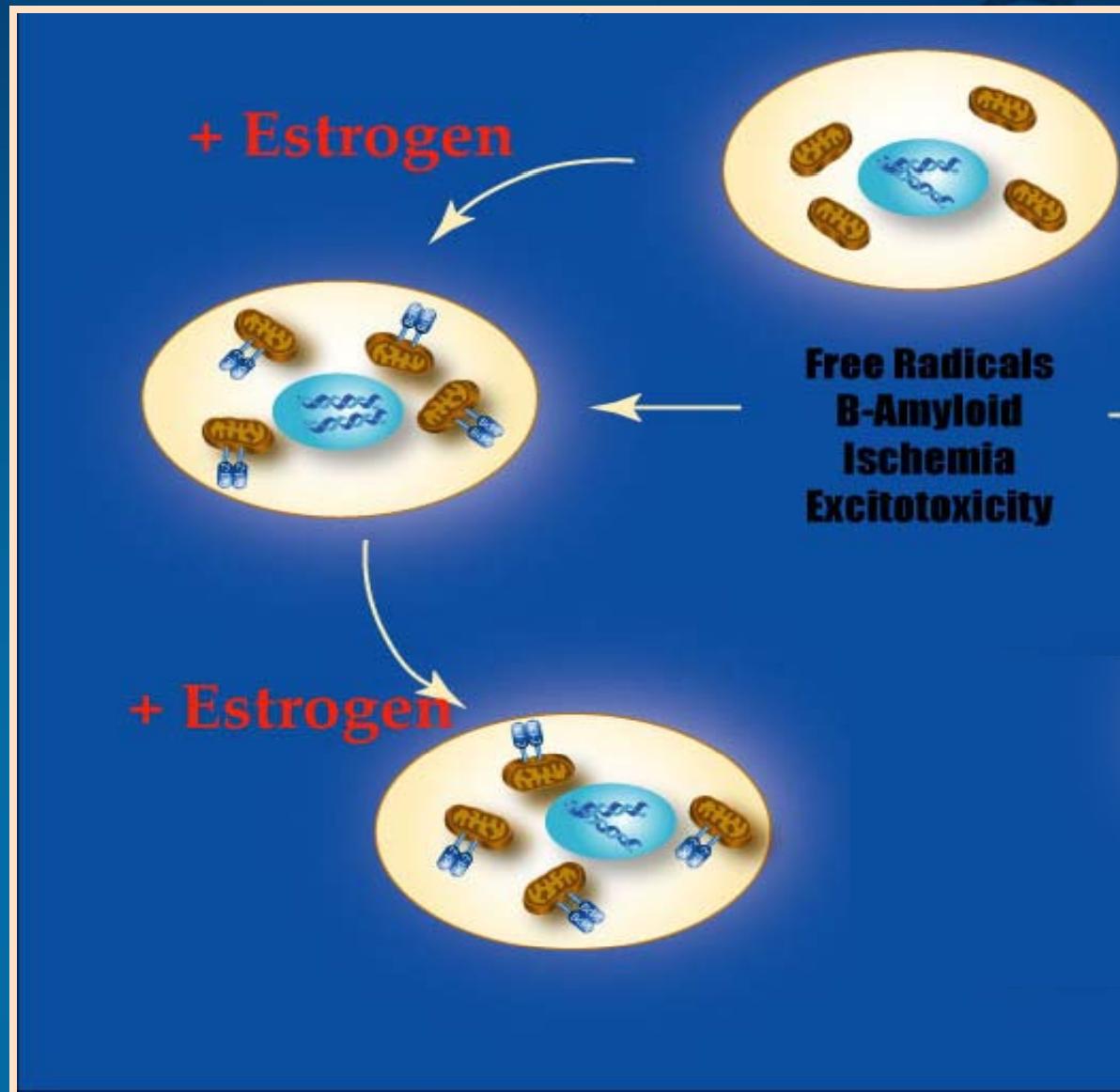
Payami H, Montee K, Grimslid H, et al.. Neurology 1996; 46 (1): 126-9

Gao S, Hendrie HC, Hall KS, et al.. Arch Gen Psychiatry 1998; 55 (9): 809-15

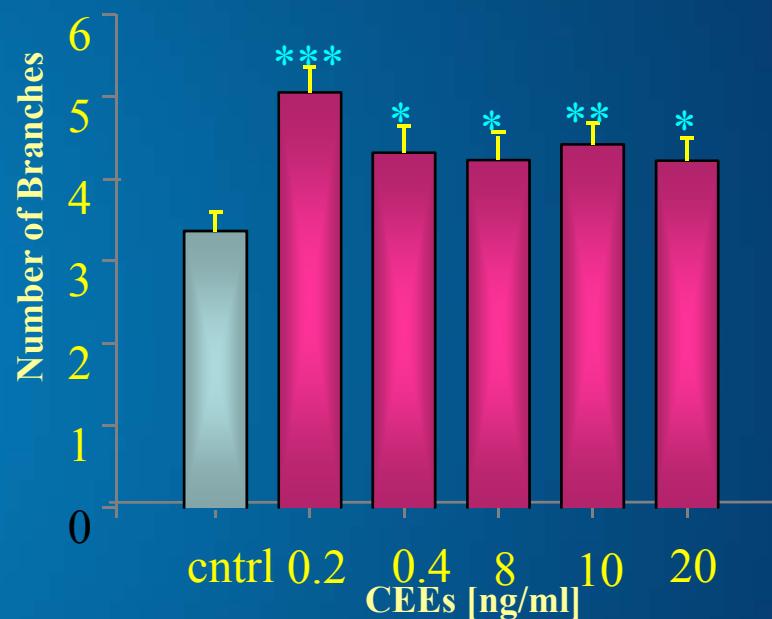
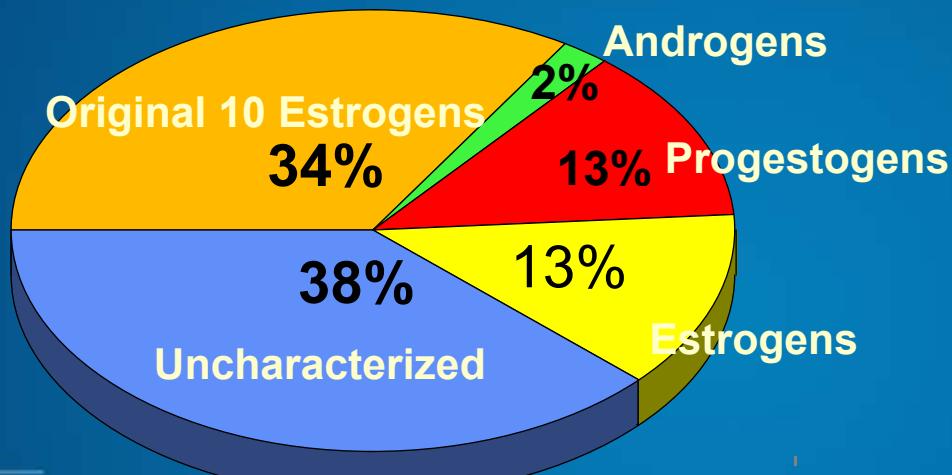
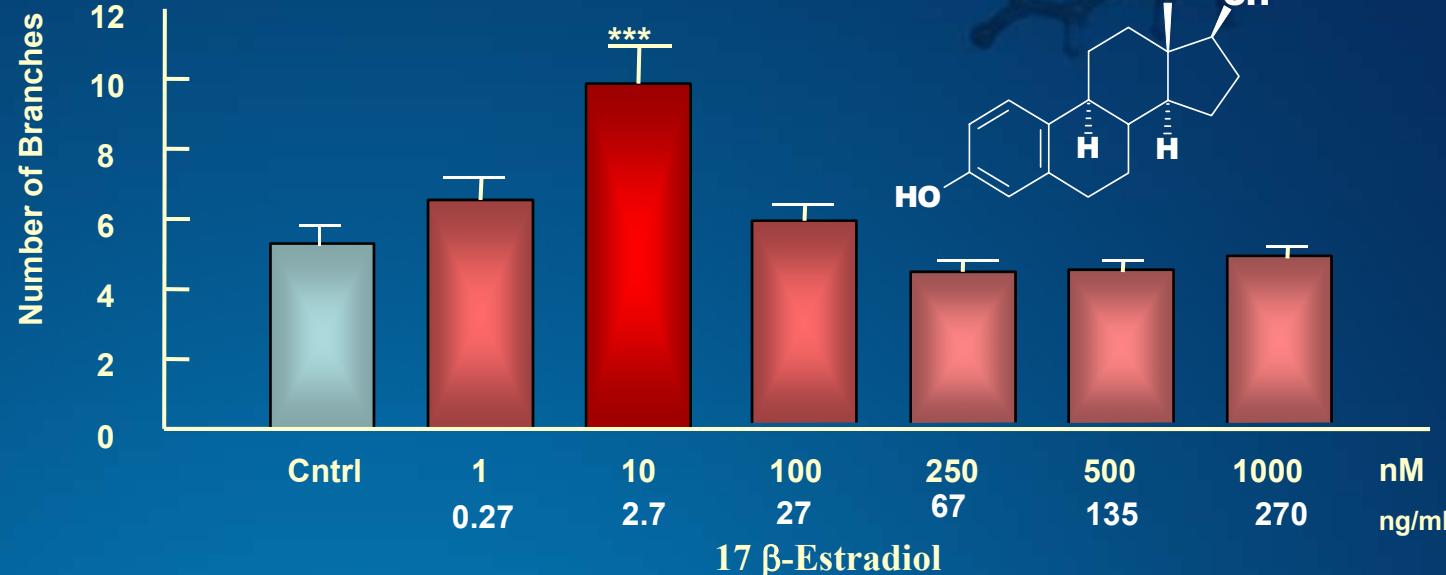
North American Menopause Society. Menopause core curriculum study guide. Basic overview, definitions, & statistics.

<http://www.menopause.org>

Healthy Cell Bias of Estrogen Action

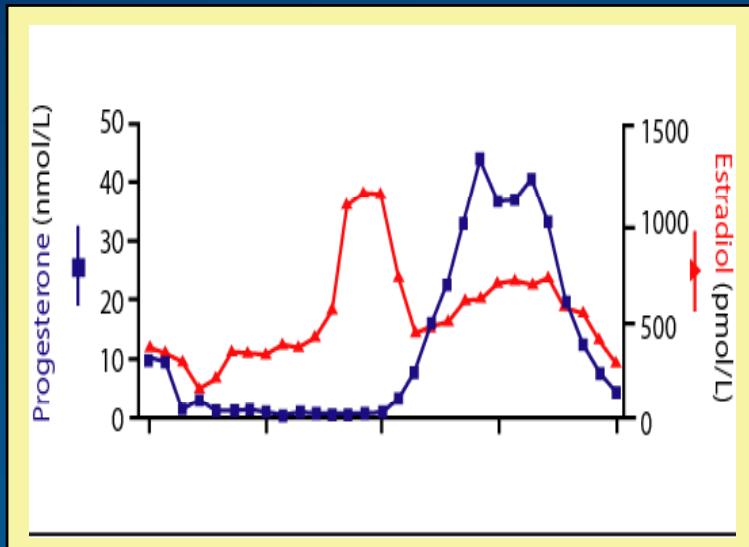


Different Estrogens Generate Different Dose Responses

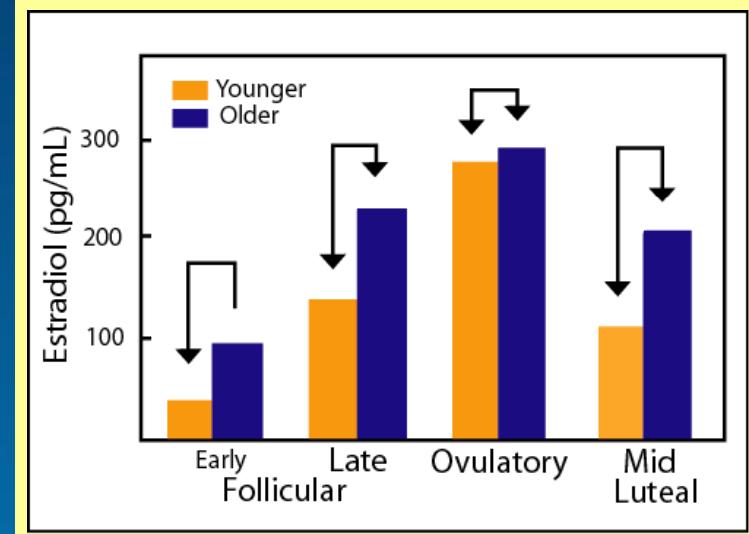


Brinton, *Neurochemical Research*, 22(11):1339-1351, 1997
Brinton, *Neurobiology of Aging* 21(3): 475-496, 2000.

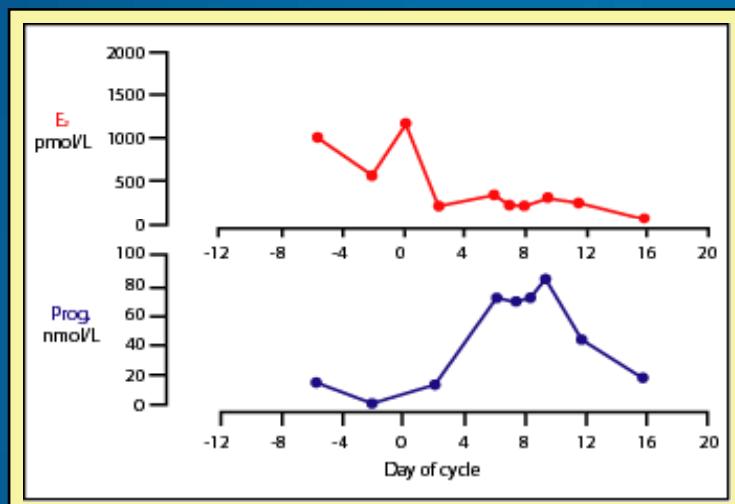
Dosing of Estrogen and Progesterone during Perimenopause



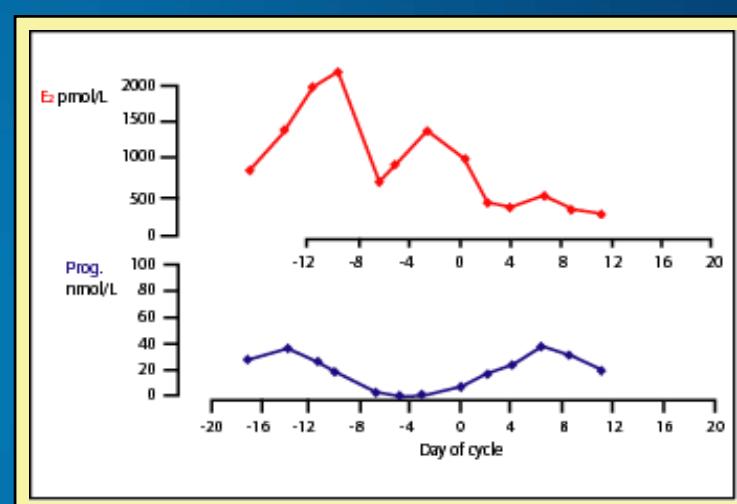
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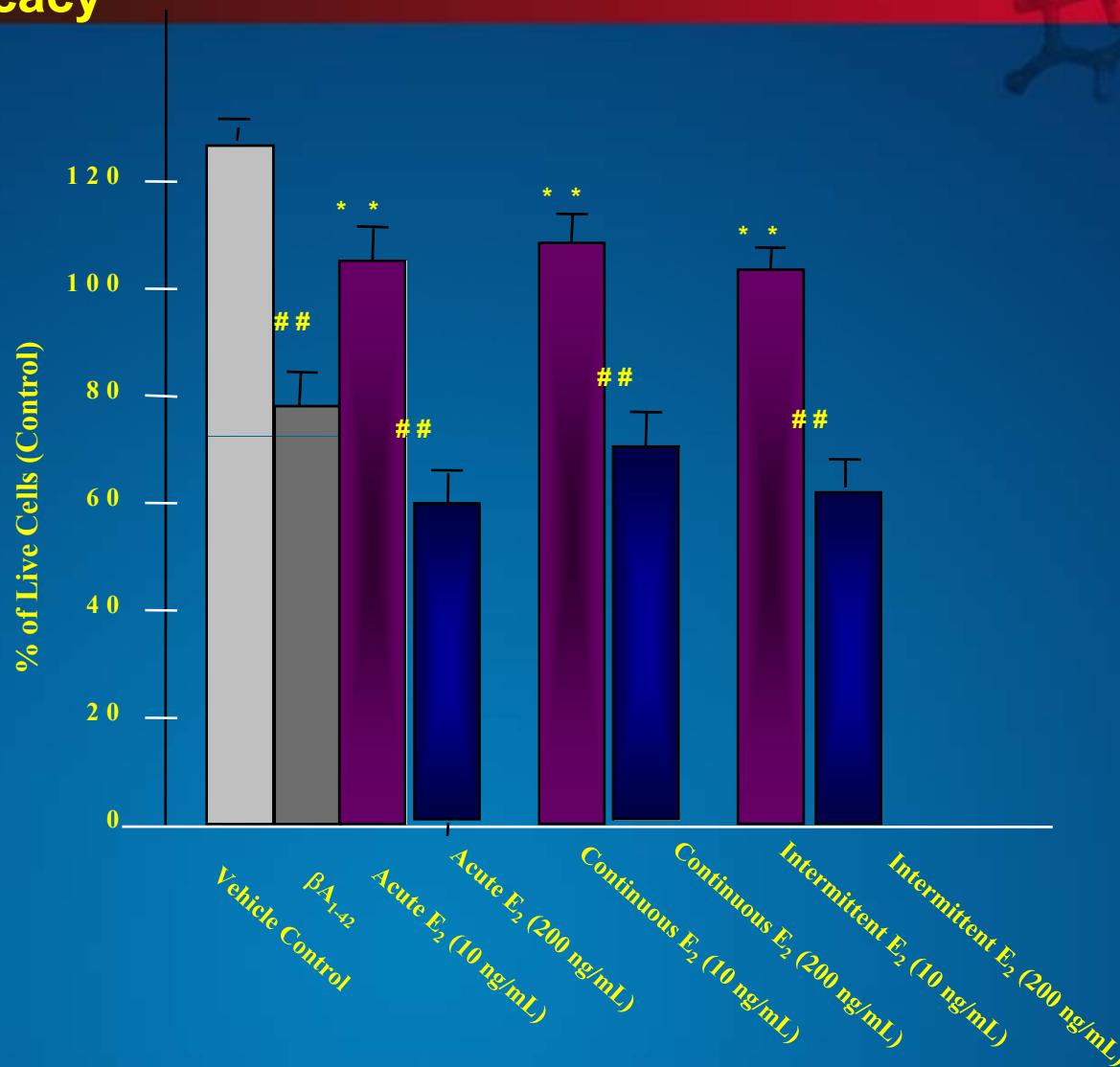
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2

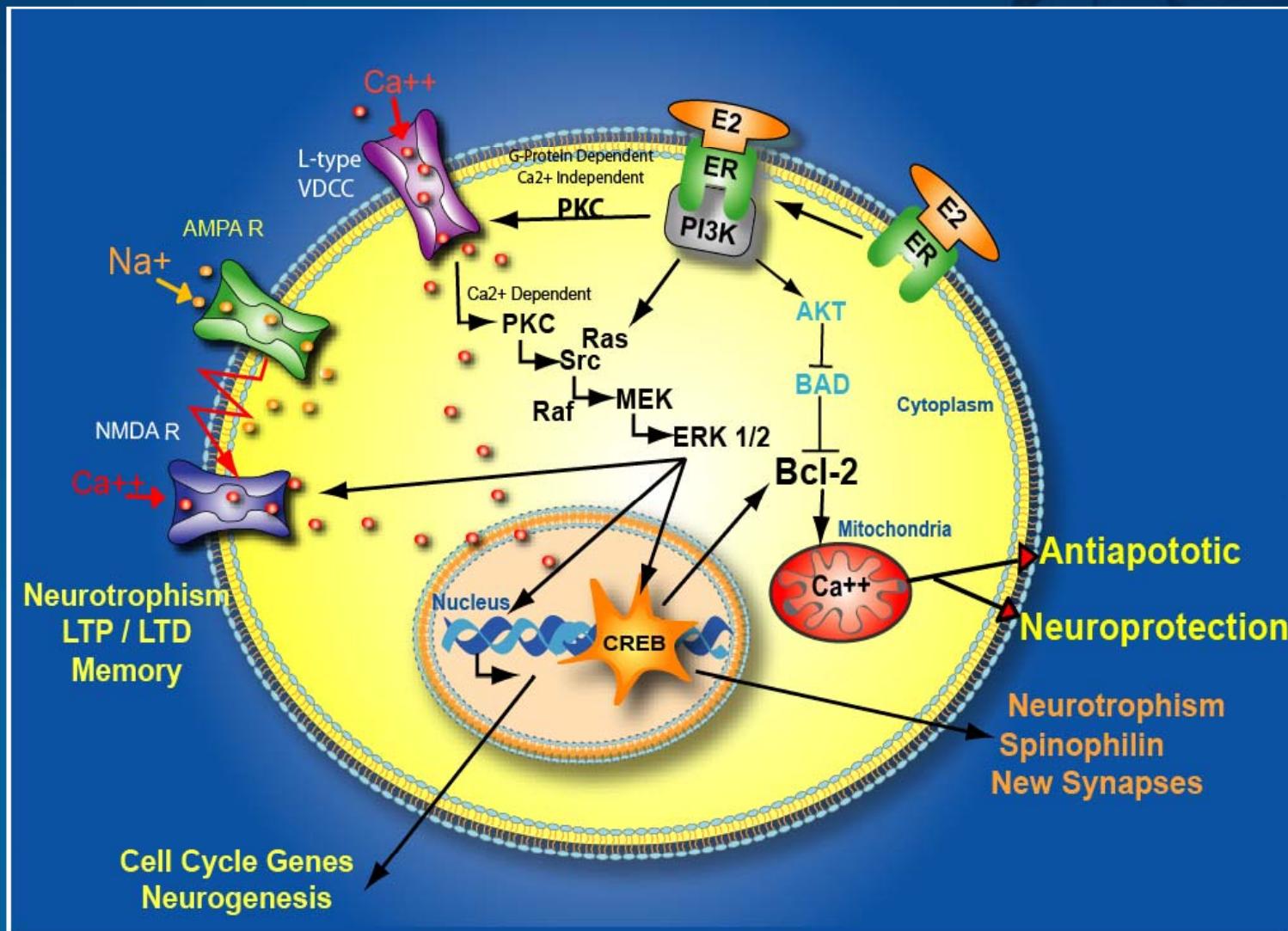


Perimenopause Simulation Estrogen Dose is the Determining Factor of Efficacy

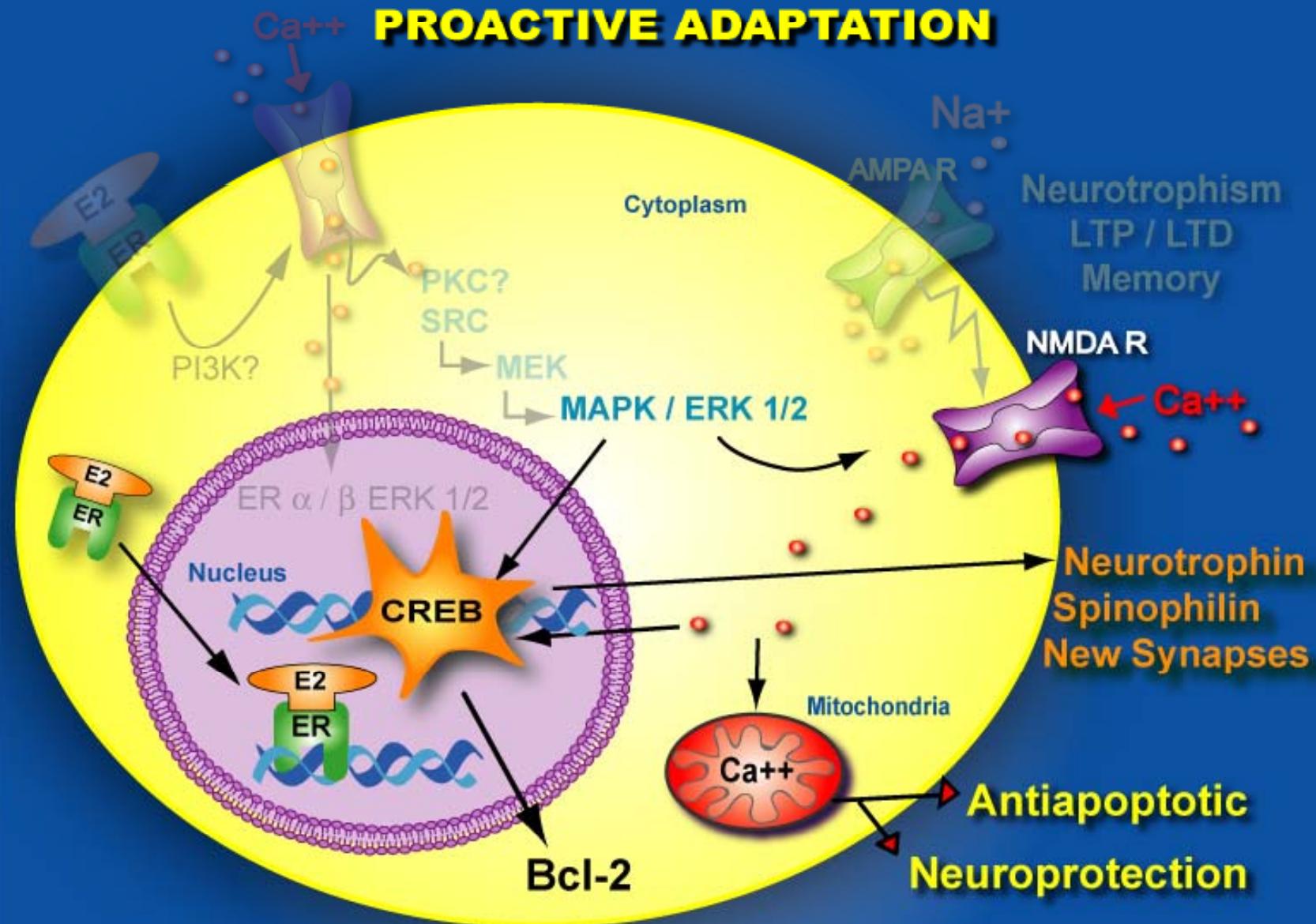


NIA: Chen, Nilsen & Brinton, Endocrinology 2006

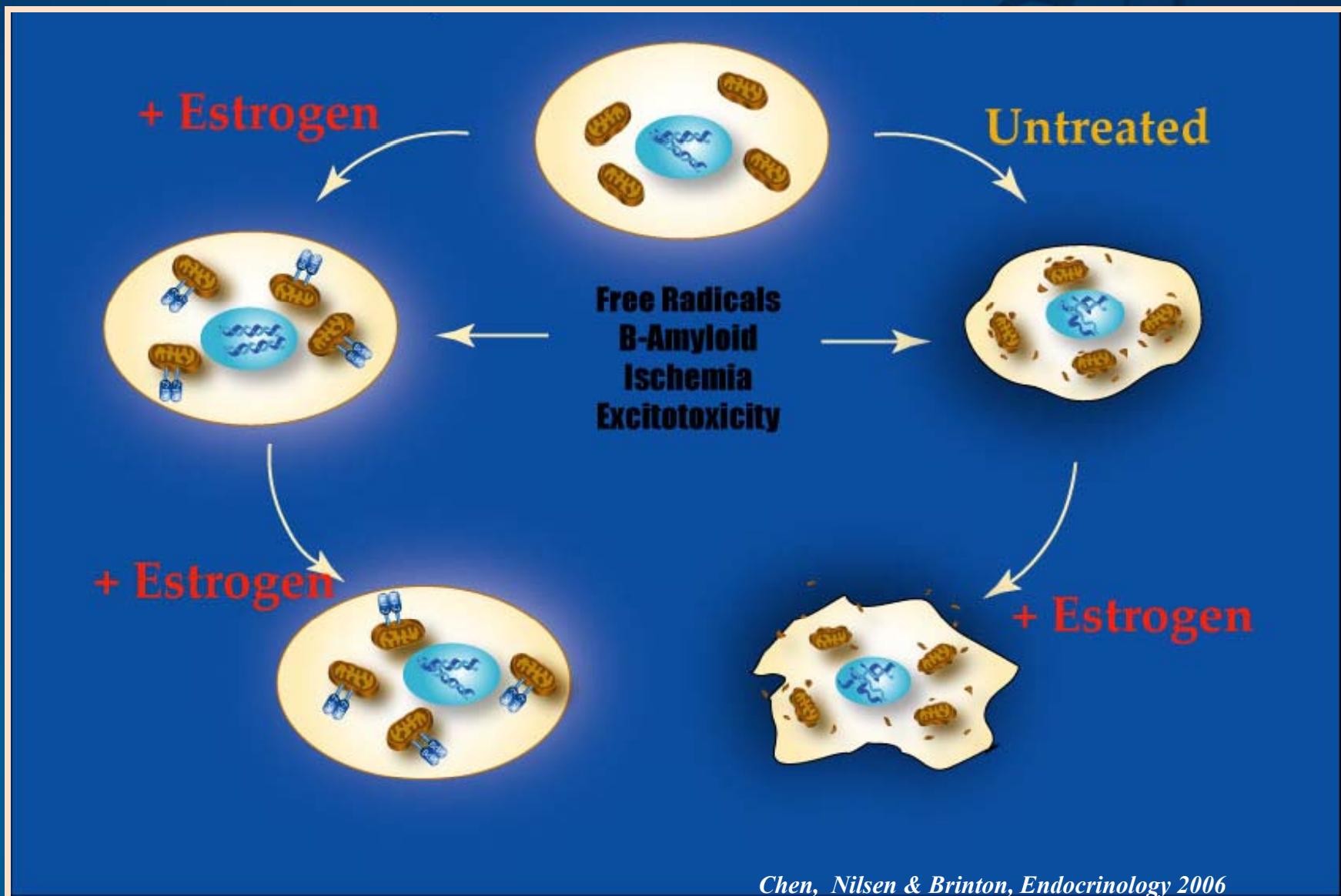
Mechanisms of Estrogen Action in Hippocampal and Cortical Neurons



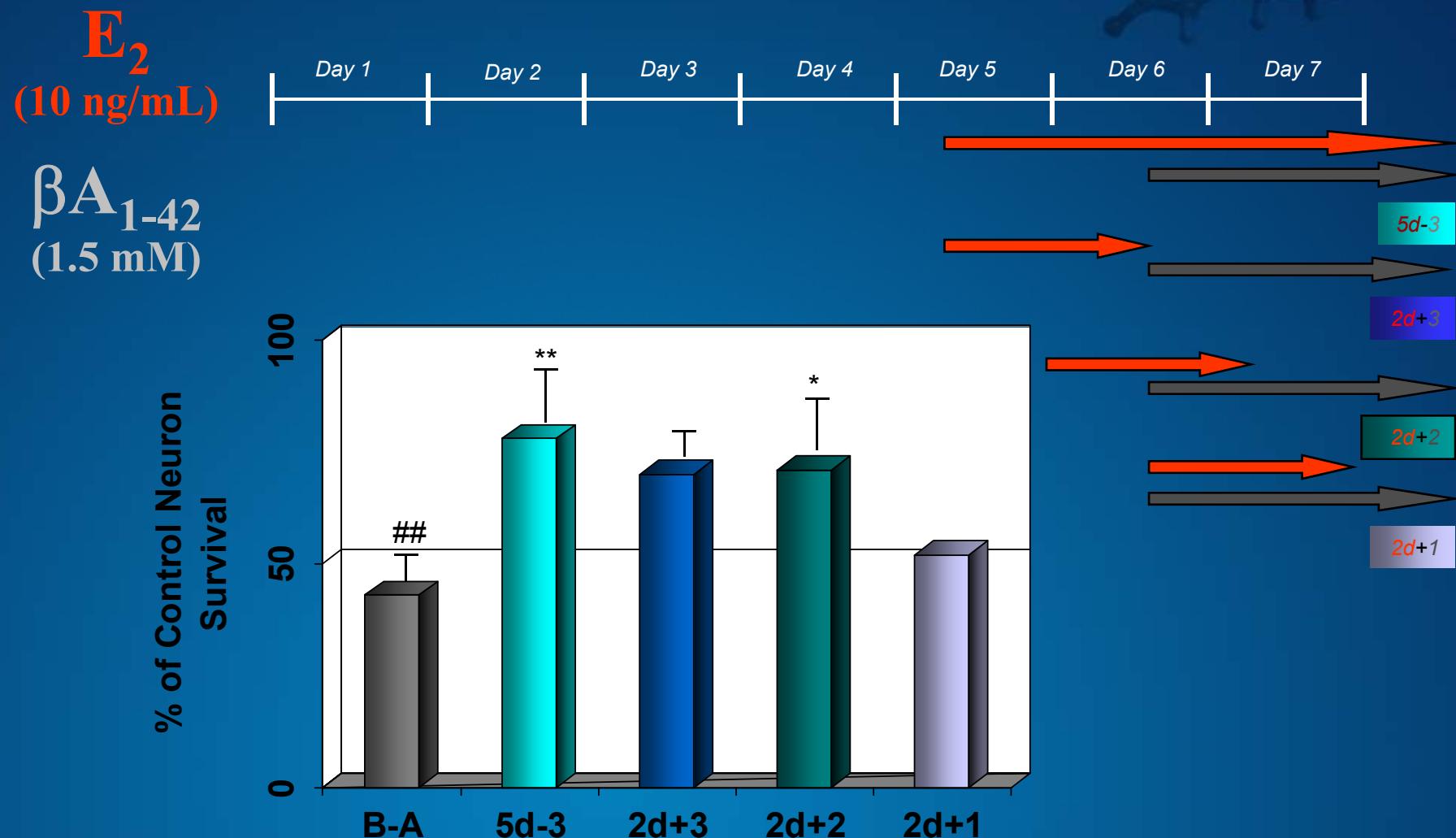
PROACTIVE ADAPTATION



Healthy Cell Bias of Estrogen Action



Estrogen is Most Effective When Present Prior To and During β A Insult



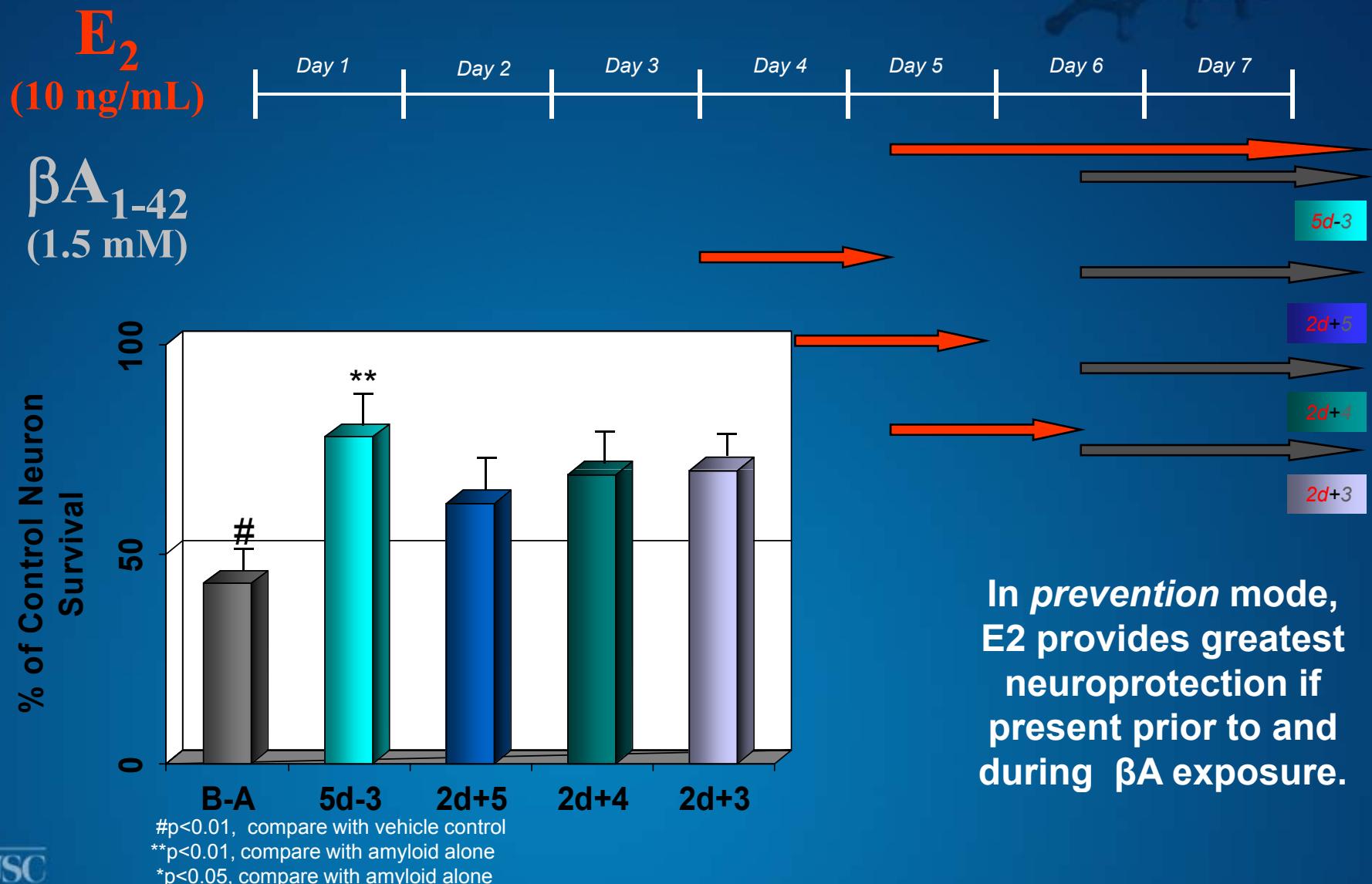
#p<0.01, compare with vehicle control

**p<0.01, compare with amyloid alone

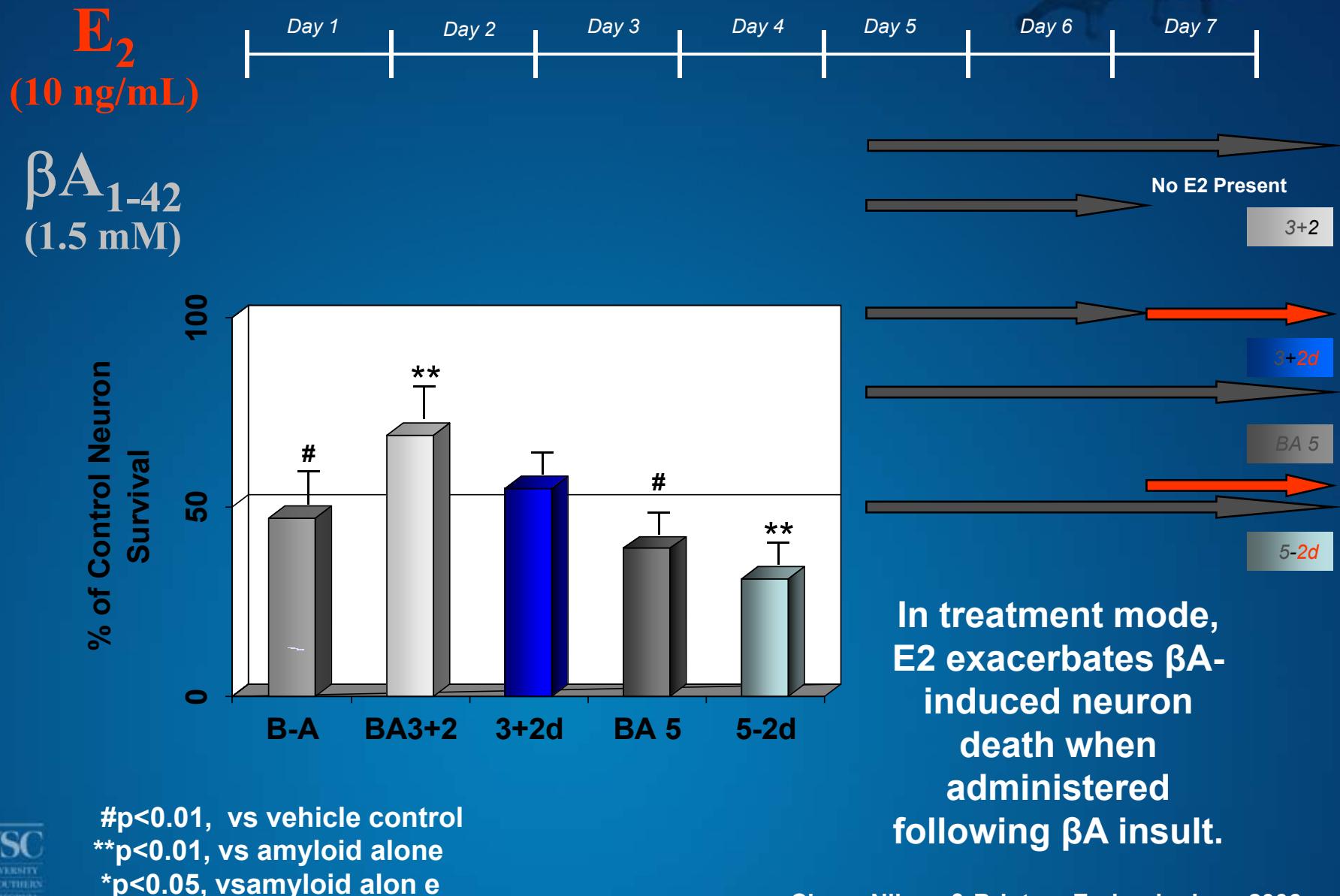
*p<0.05, compare with amyloid alone

Chen, Nilsen & Brinton, Endocrinology 2006

Window of Opportunity for Estradiol NeuroProtection Against β -Amyloid

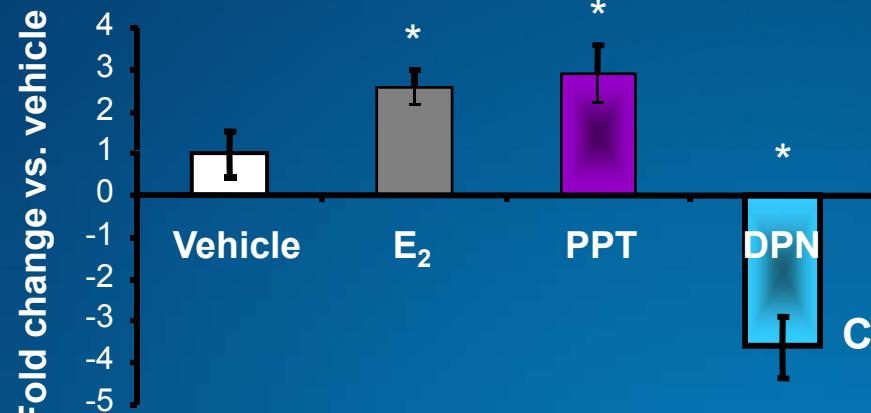


Efficacy of Estradiol Treatment to Reverse β Amyloid-Induced Degeneration

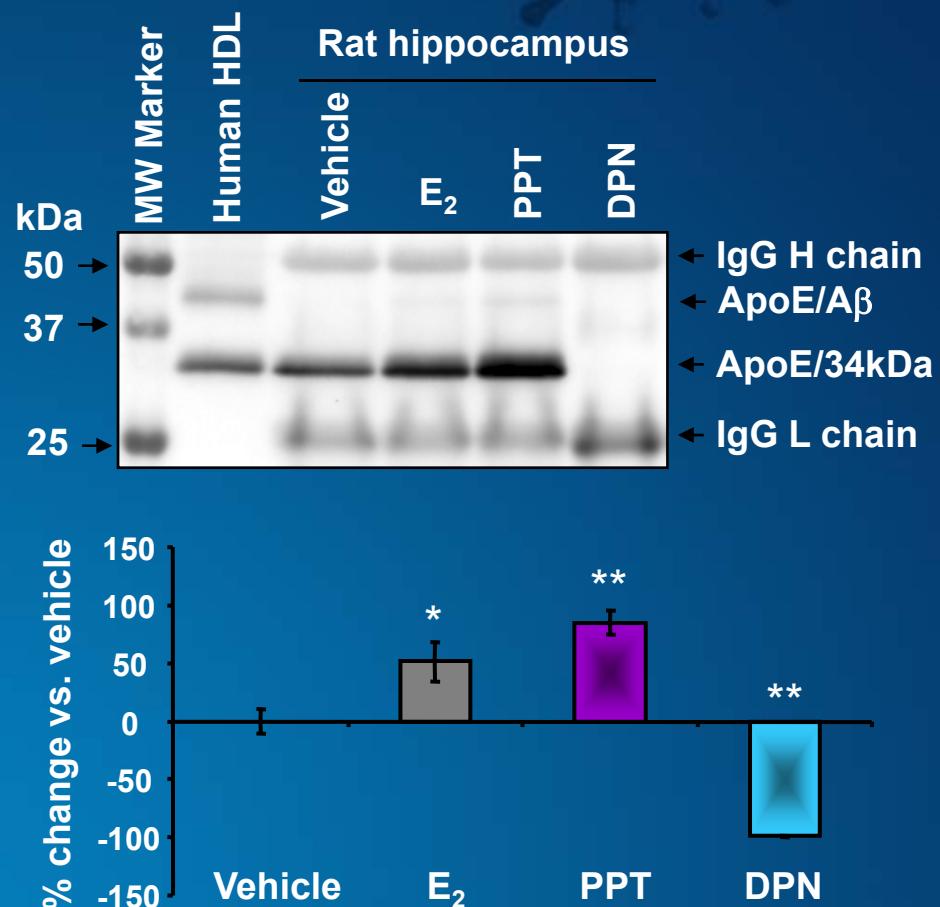


Estrogen Receptor Regulation of ApoE Expression: *In Vivo*

A

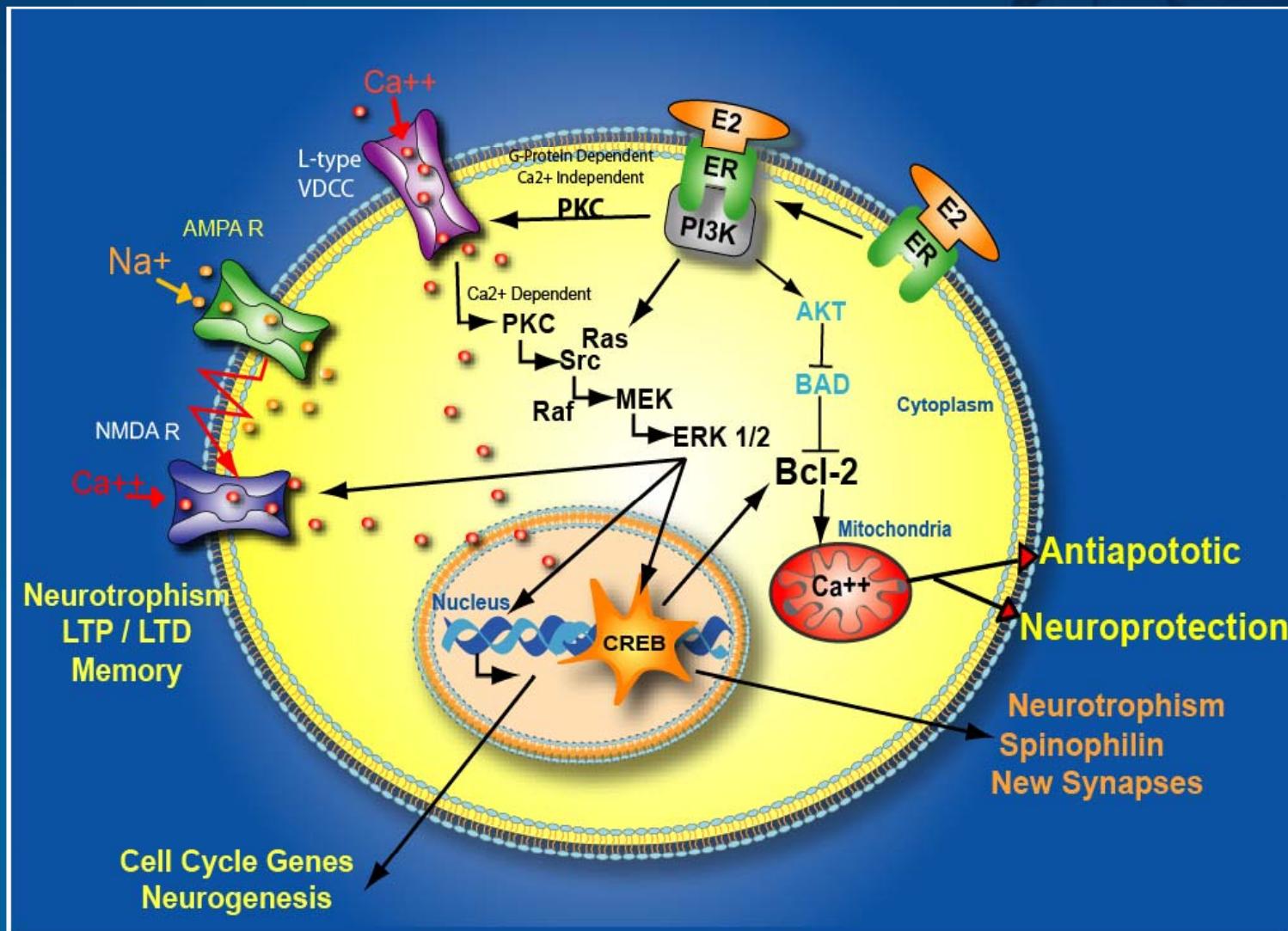


B

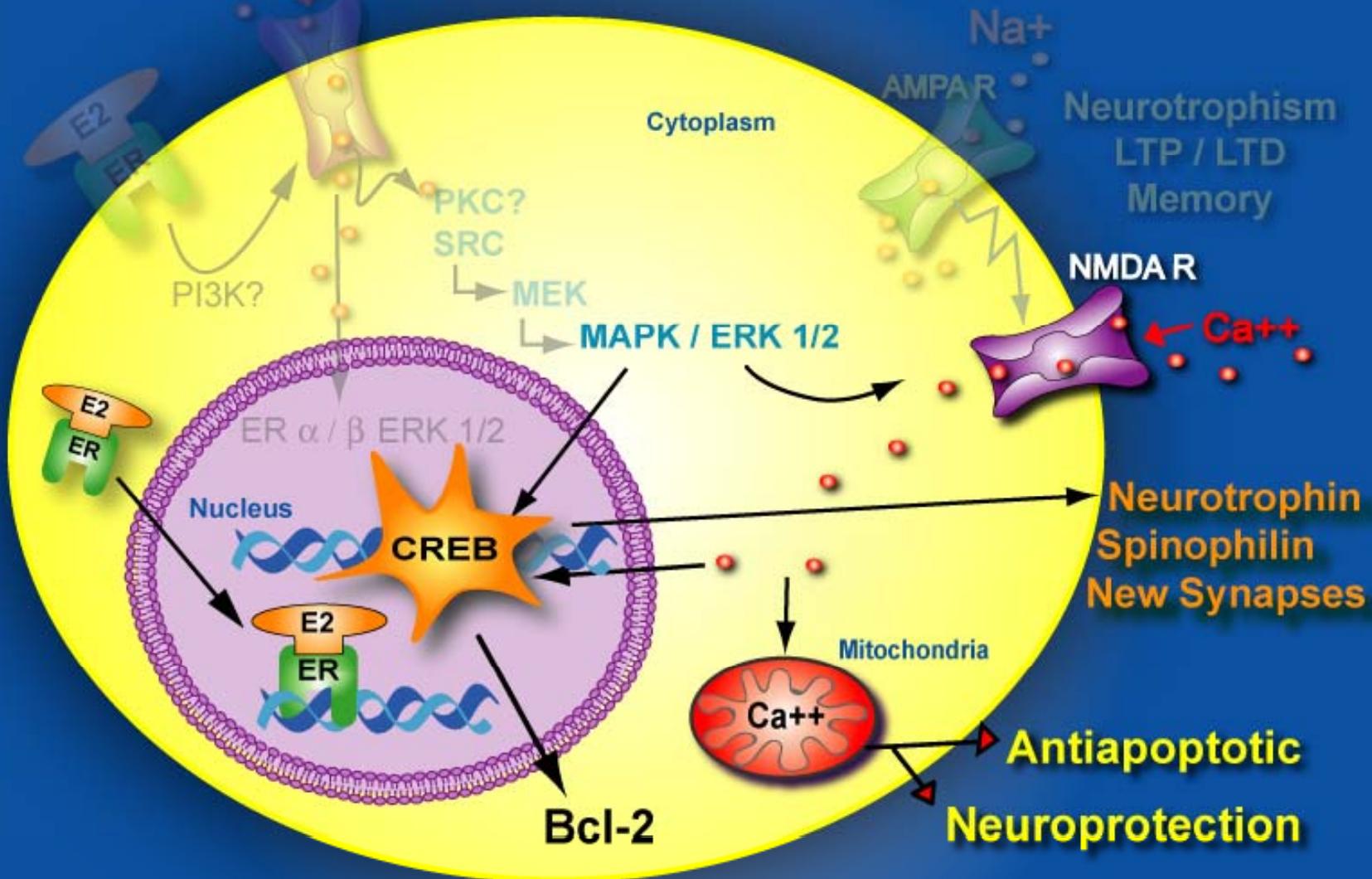


C

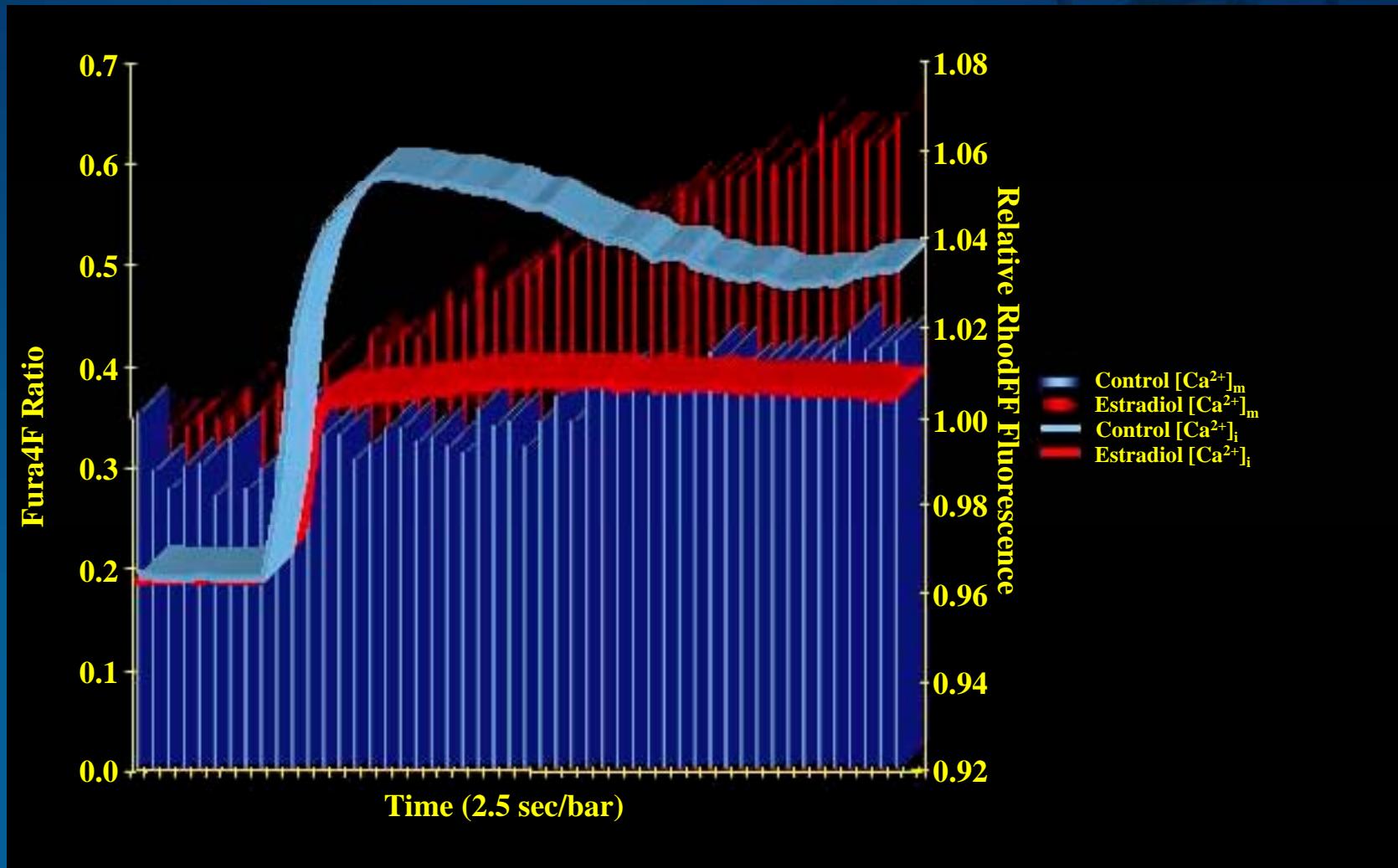
Mechanisms of Estrogen Action in Hippocampal and Cortical Neurons



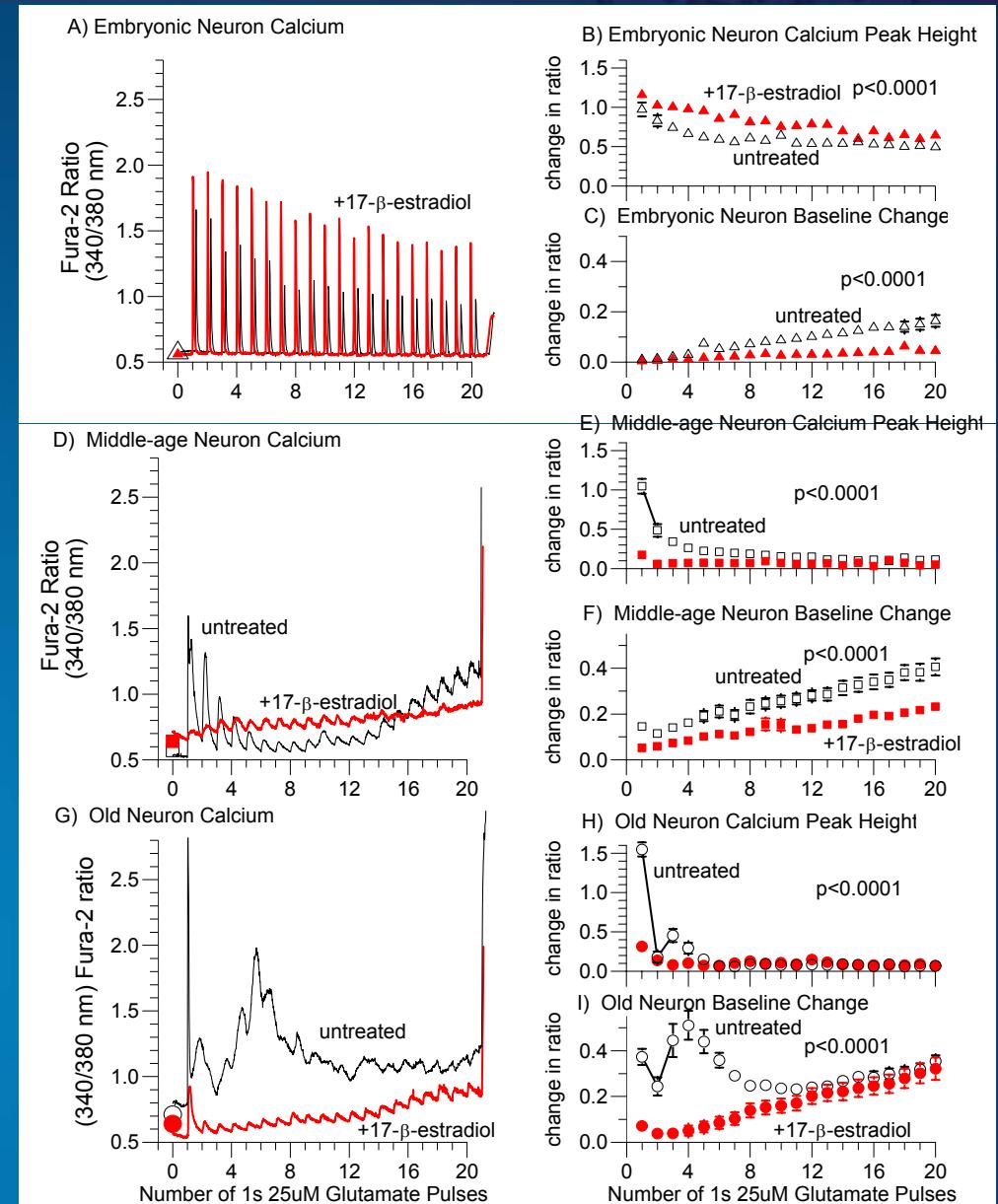
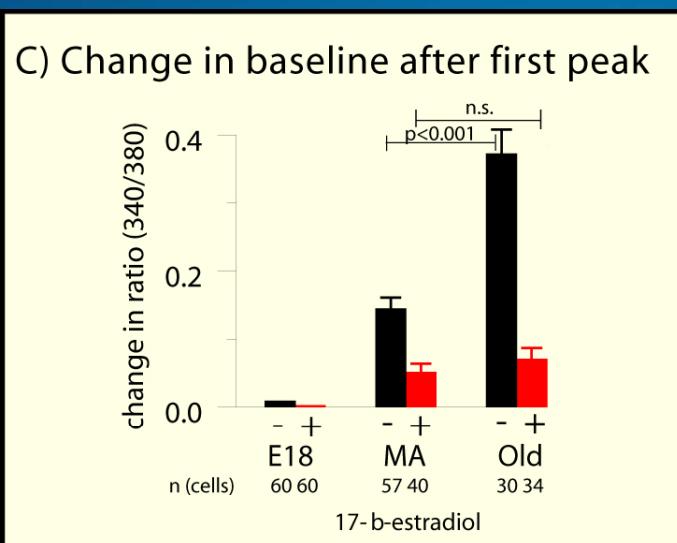
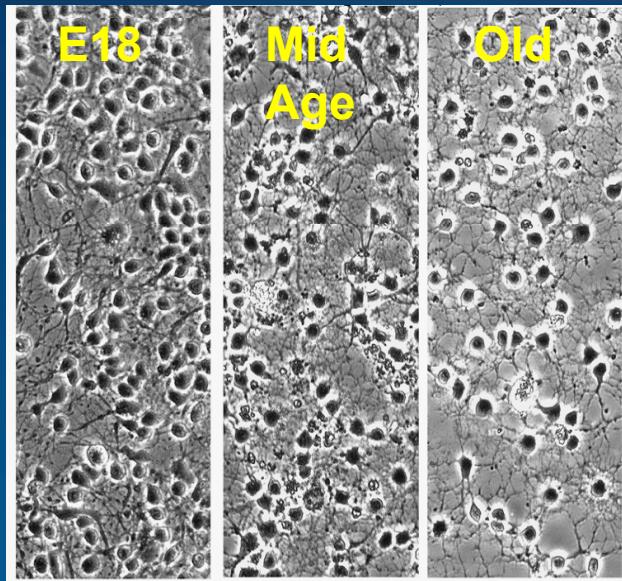
PROACTIVE ADAPTATION



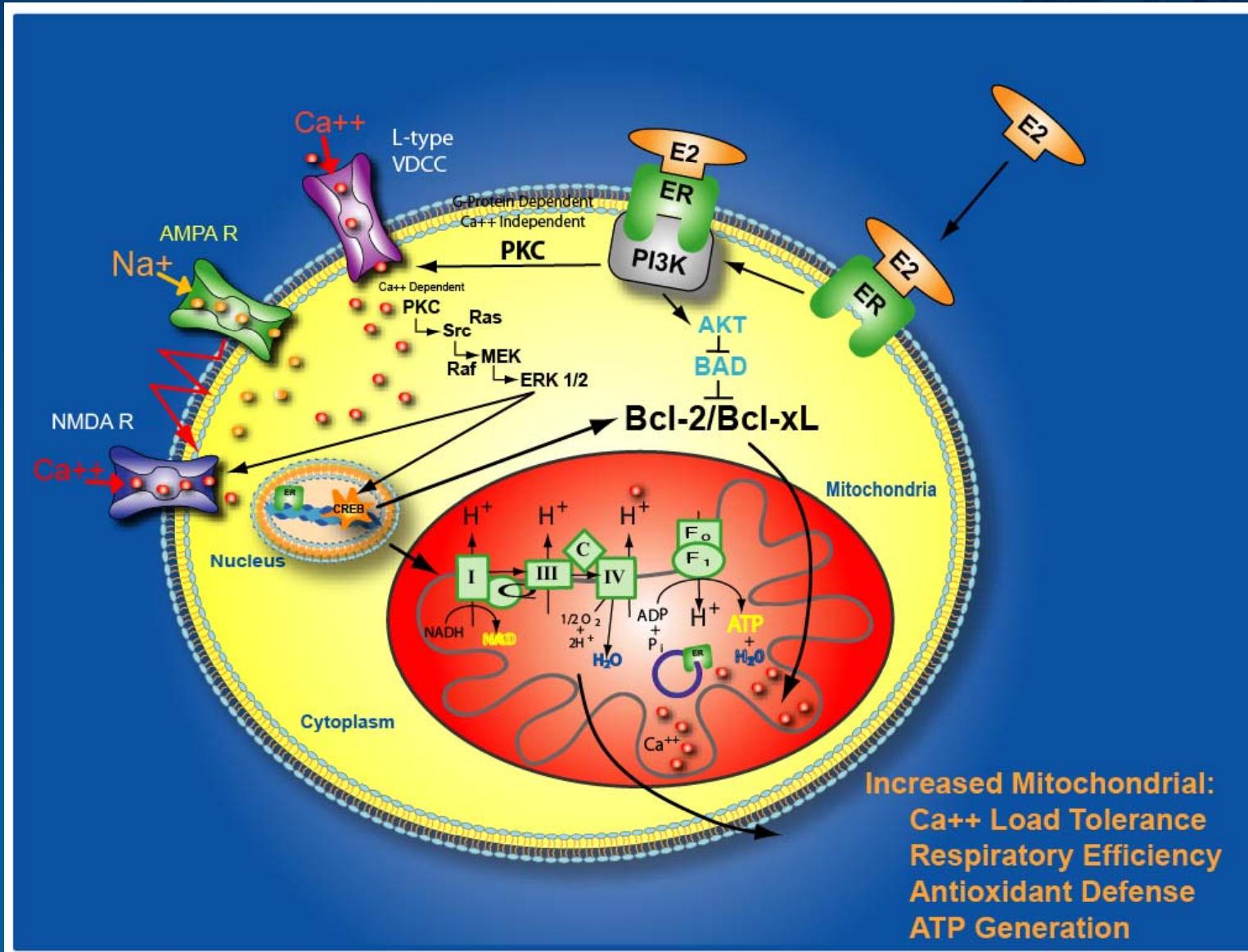
17β -Estradiol Promotes Mitochondrial Sequestration of Calcium



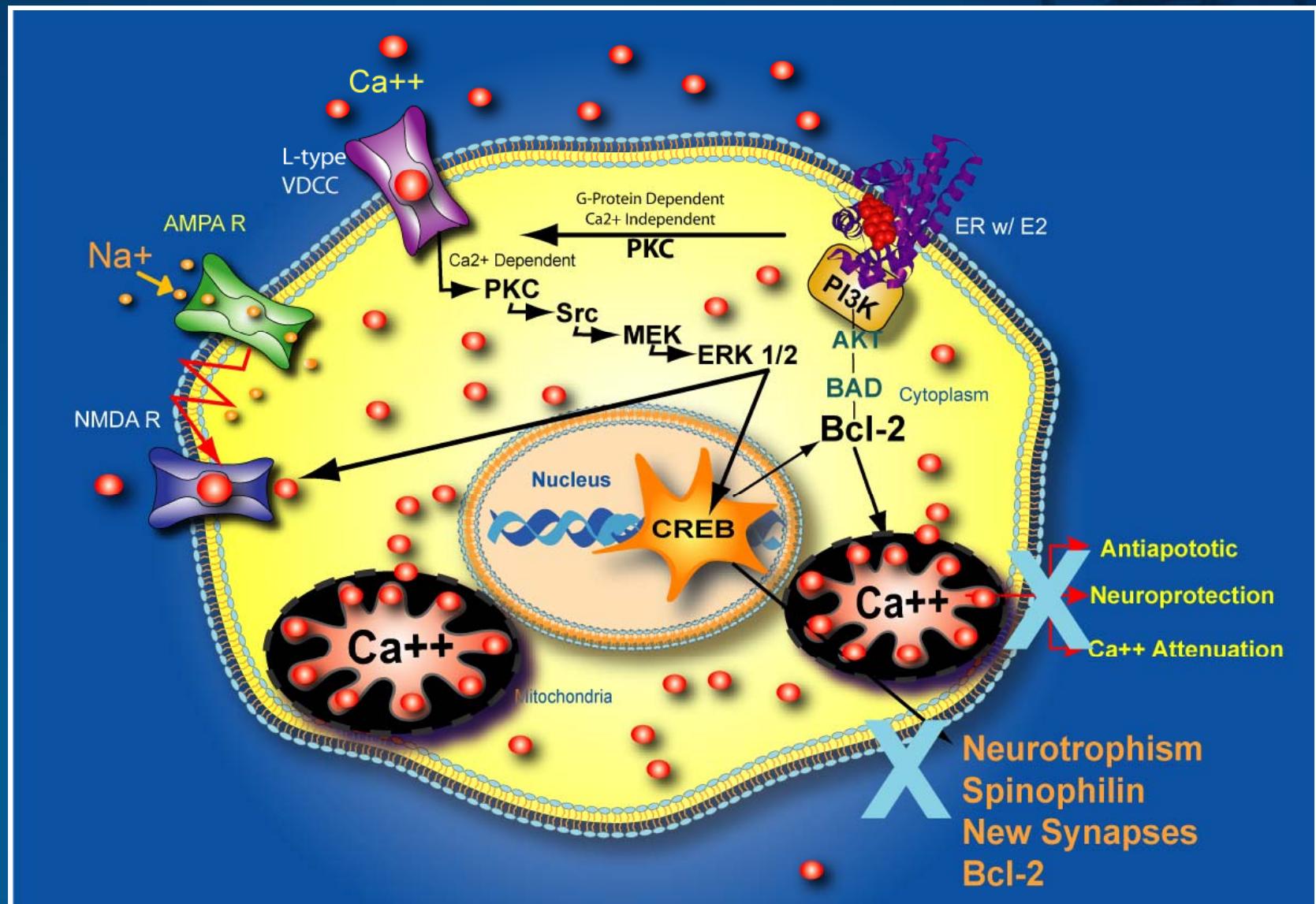
Estrogen ProActively Maintains Calcium Homeostasis During Aging



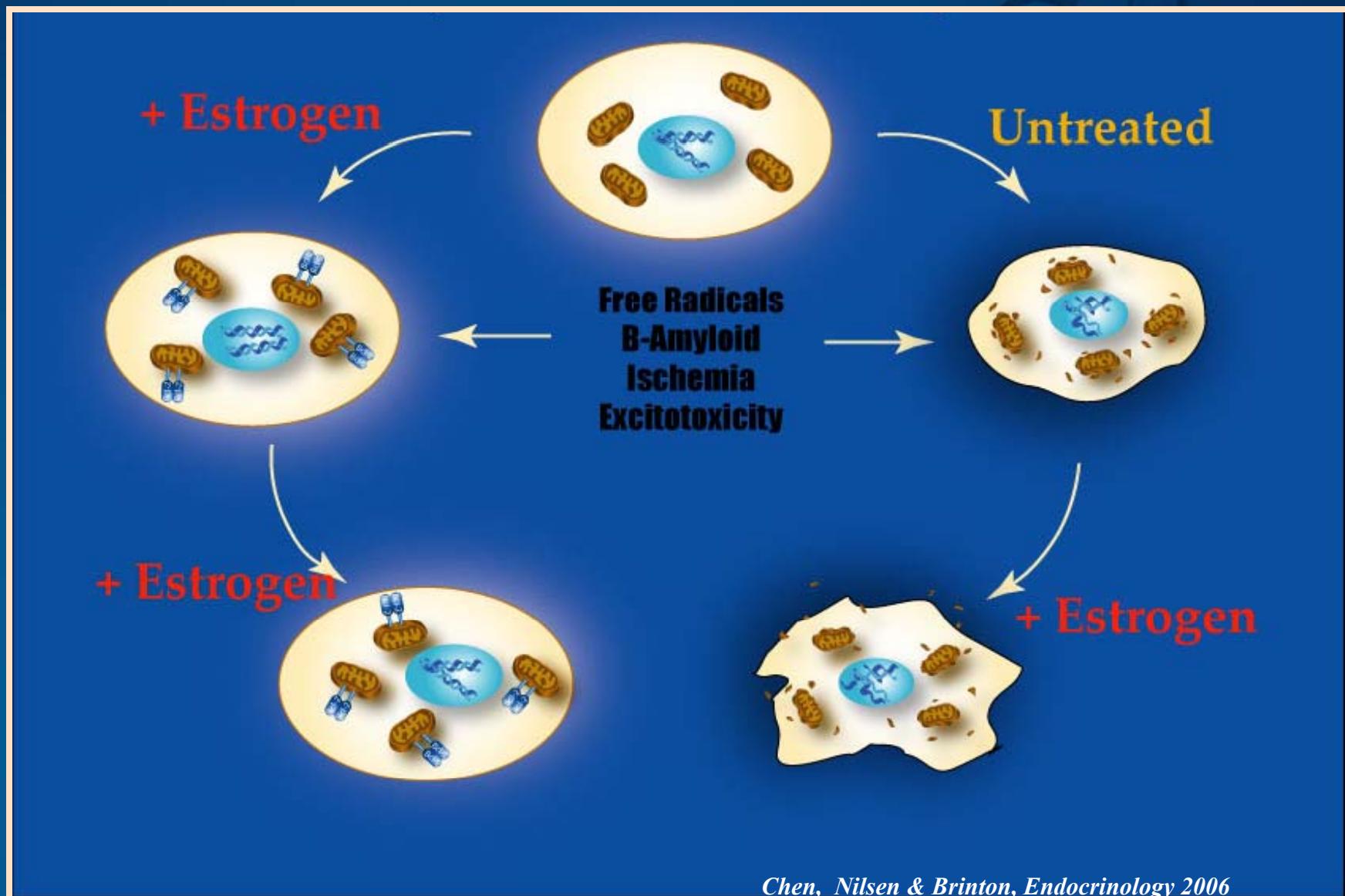
Estradiol-Induced Neuroprotective Signaling Pathways Converge On Mitochondria



Sequestration of Calcium into Mitochondria: The Achilles Heel of Estrogen Action?



Healthy Cell Bias of Estrogen Action

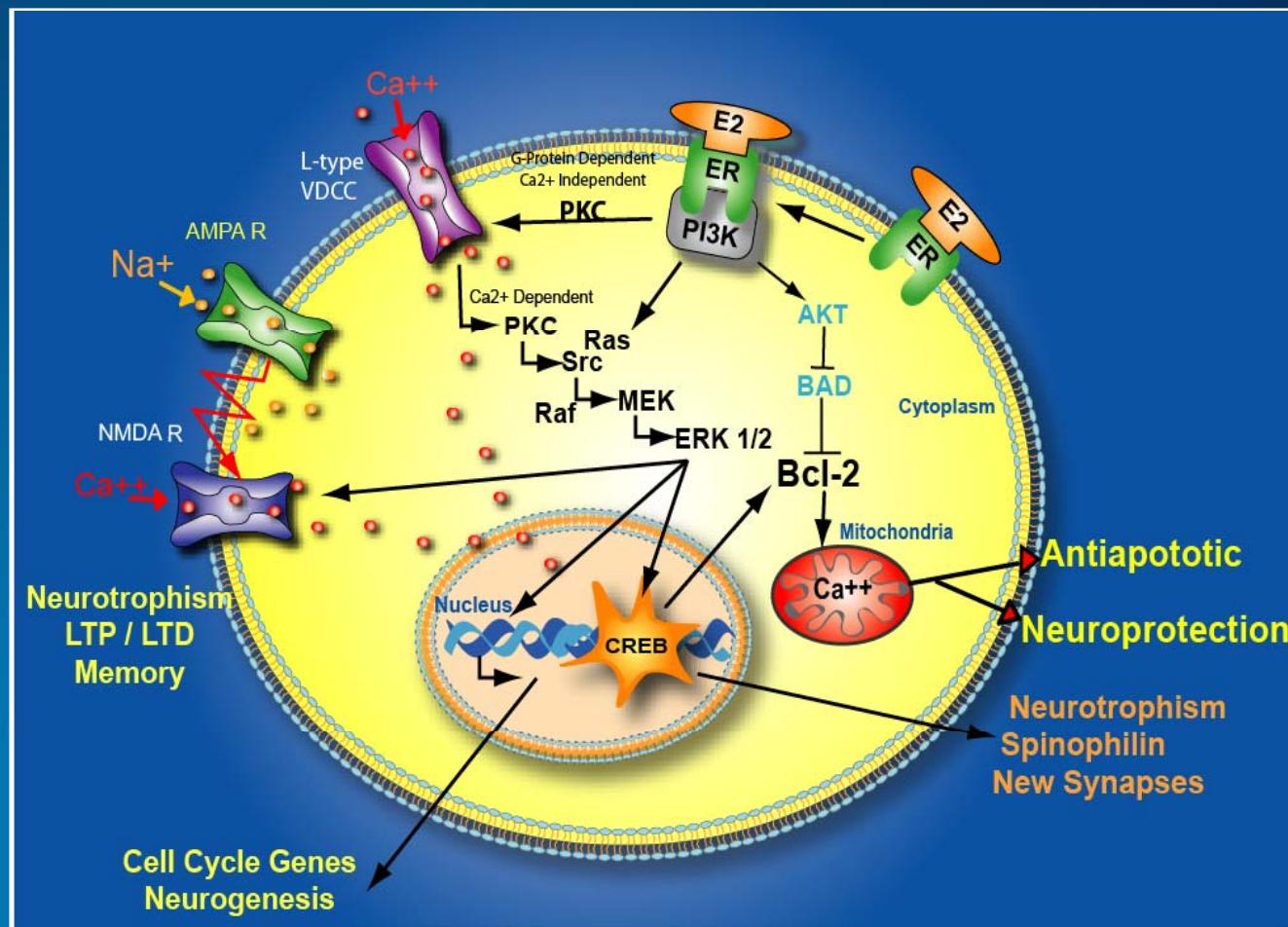


Chen, Nilsen & Brinton, Endocrinology 2006

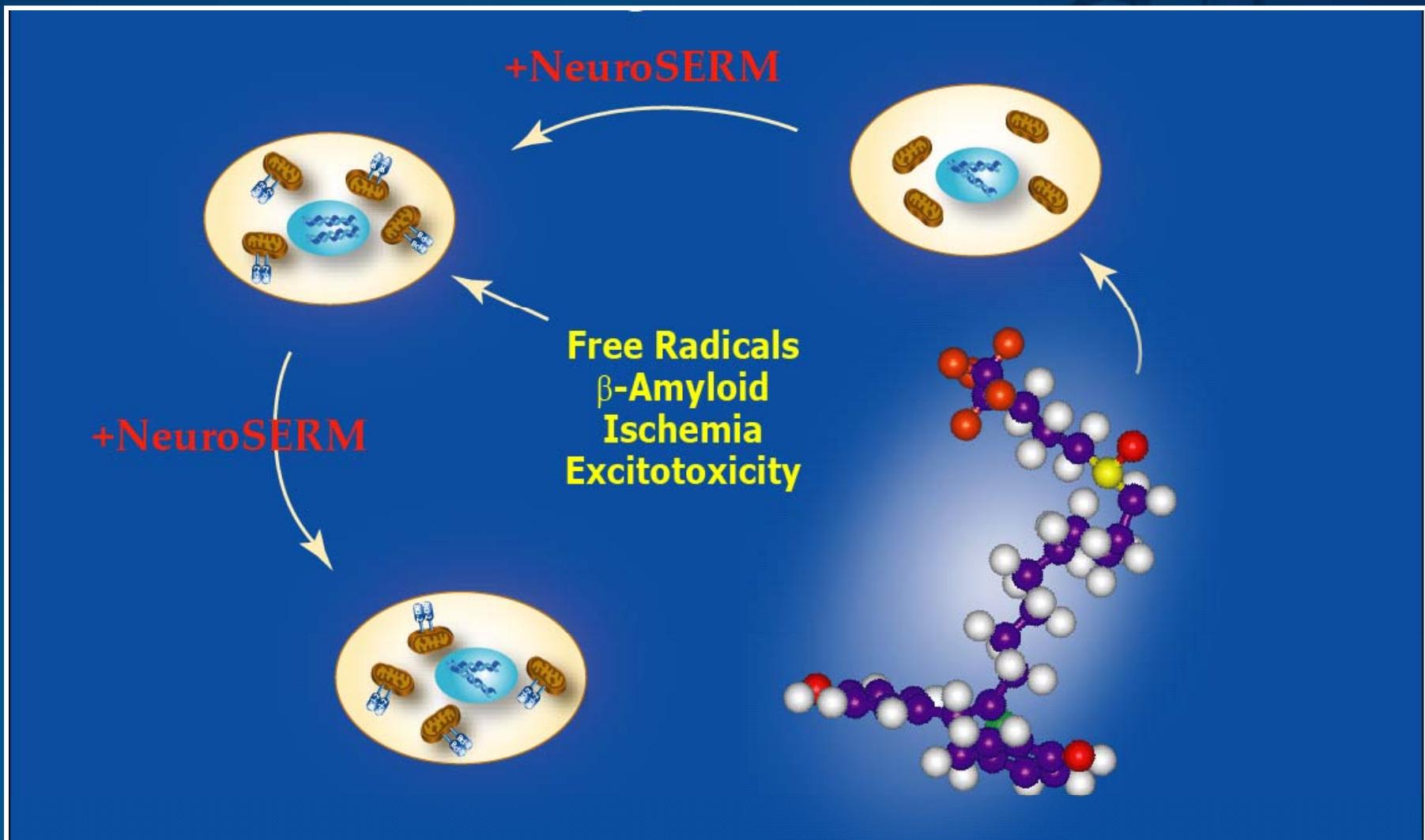
Mechanisms of Estrogen ProActive Adaptation Action in Hippocampal and Cortical Neurons

Estrogen

- Activates both MAPK and Akt.
- Convergence of neuroprotective mechanisms onto mitochondria.
- Regulates mitochondrial proteome to promote efficient and enhanced mitochondrial respiration/ ATP generation.
- Healthy bias of benefit.
- Calcium dependency may be Achilles heel.



NeuroSERM / PhytoSERM Prevention of Age-Related Neurodegeneration



Brinton Research Team, Collaborators and Supporters

Brinton Laboratory

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- Dr. JunMing Wang
- Dr. Liqin Zhao
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- Dr. Paolo Mannella
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- Dr. James Kerwin
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- Jia Yao
- Paige Chung
- Jennifer Mao
- Eva Sogenstein
- Angela Hongtongsak
- Kathy Cho
- Jimmy To
- Crystal De La Cruz
- Alison Morales



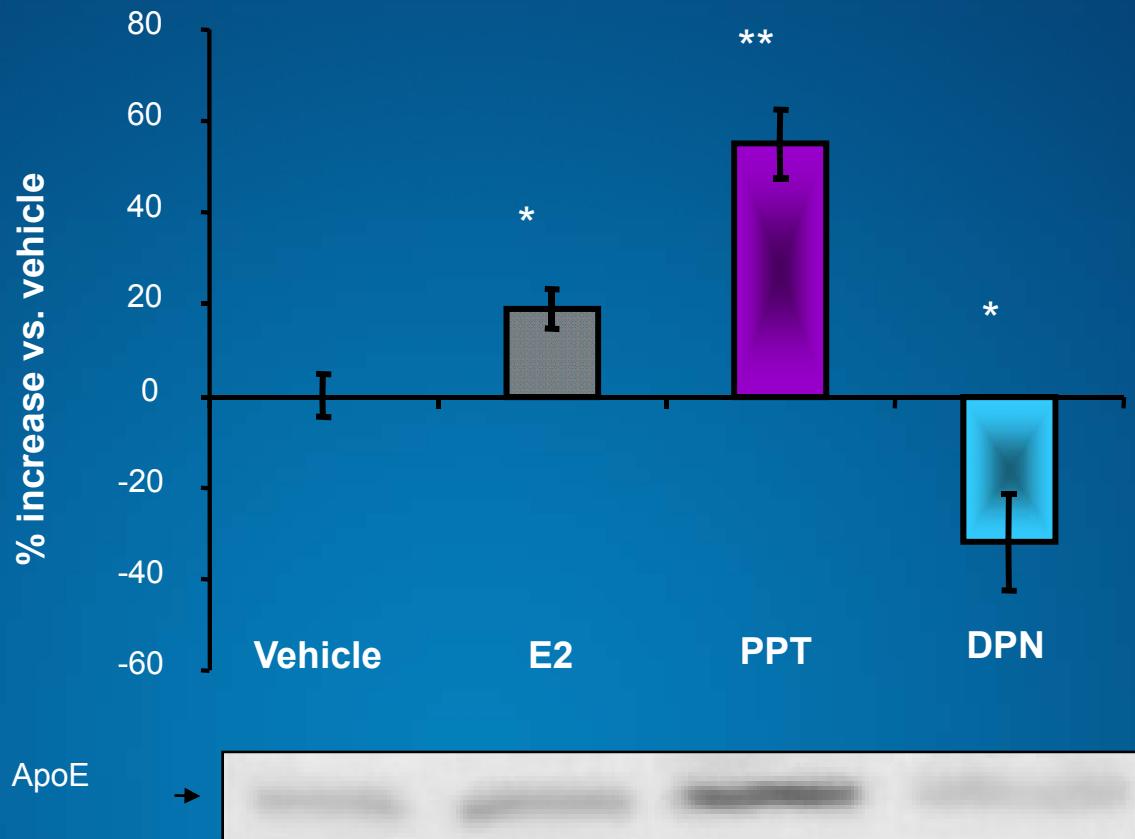
Collaborators

- Dr. Theodore Berger
- Dr. Richard Thompson

Research Sponsors

- National Institute of Aging
- National Institute of Mental Health
- Institute for the Study of Aging / AD
- Kenneth T. and Eileen L. Norris Foundation
- NIMH Chemical Synthesis and Drug Supply

Estrogen Receptor Regulation of ApoE Expression: *In Vitro*



Wang, Irwin and Brinton, PNAS, 2006