

Selegiline
Mimics Preconditioning Induction of
the Redox Protein Thioredoxin Against
MPP⁺-induced Neurotoxicity

C. C. Chiueh, Ph.D.

Pharmacy School
Taipei Medical University
Taipei, Taiwan

Helsinki Drug Research
June 9 2008

Helsinki 9 pm Sun Light



1975-2005 NIH
A 30-Yr Research Career

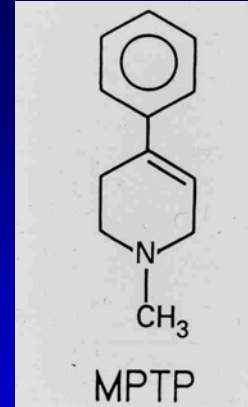


Question

- Why (-)-deprenyl (selegiline) protects against both MPTP and MPP⁺ neurotoxicity?
 - MAO-B Inhibitor
 - Inhibition of the conversion of MPTP to MPP⁺
 - Non-MAO-B Effect
 - Activation of cellular compensatory Trx defense system

Introduction

- Age-dependent Increase in Non-heme Iron in Human Basal Ganglia
- Age-dependent Progressive Degeneration of pigmented Nigral Neurons
- The Mixture of Dopamine, Iron and Oxygen
 - Free radical generation
 - Melanin formation (*blocked by selegiline)
 - Neurodegeneration
 - Protection by GSNO (*Rauhala et al., 1998)

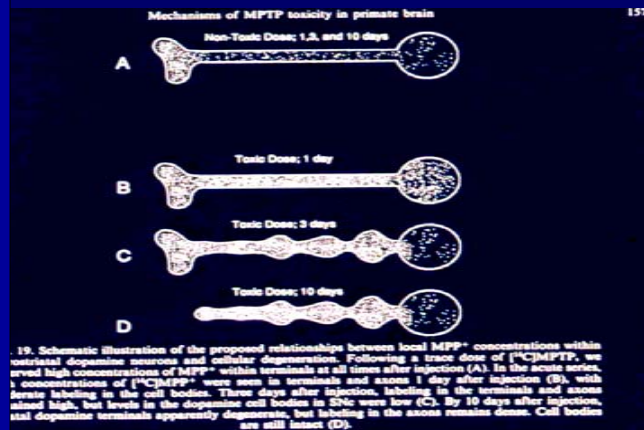


MPTP: a Man-made Neurotoxin Which Causes Parkinsonism.

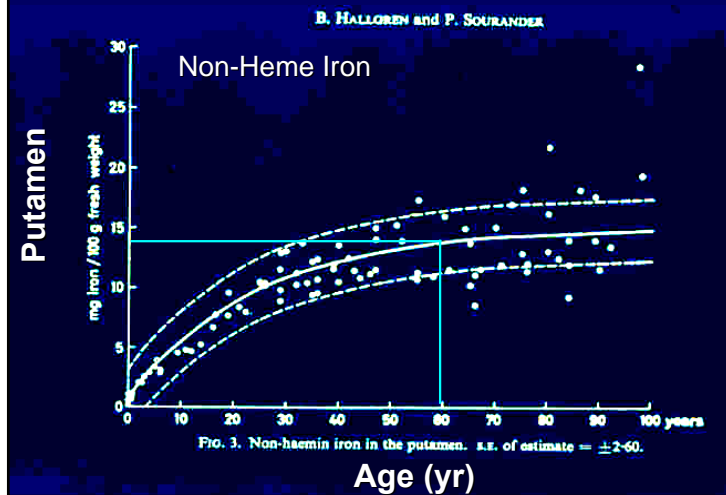
1. A young addict in DC
2. Several drug abusers in California
3. A pharmaceutical chemist in Denmark

1-Methyl-4-Phenyl-1,2,3,6-TetrahydroPyridine

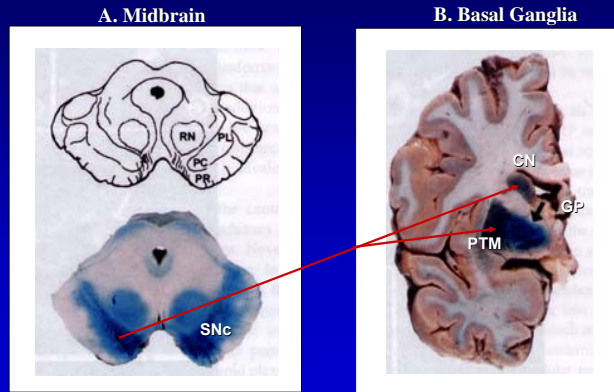
MPTP Induces Retrograde Degeneration



Accumulation of Iron in Human Putamen

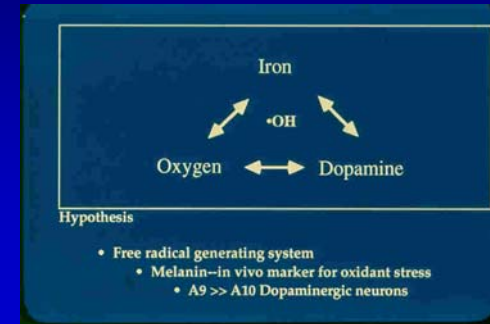


MPTP Causes a Selective Injury of Iron-Enriched Nigrostriatal Dopaminergic Neurons

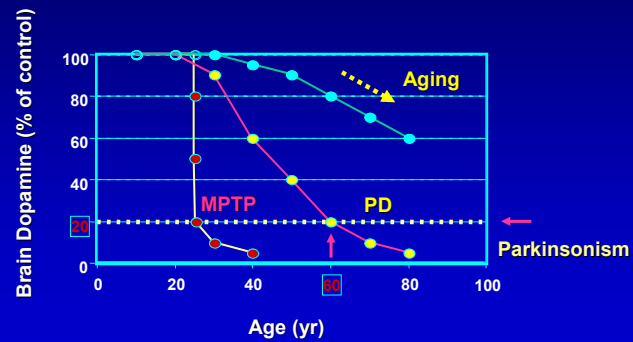


Nigrostriatal Dopaminergic System

Iron-induced Dopamine Auto-oxidation and Selective Oxidative Stress of Nigral Neurons



Progressive Neurodegeneration in Brain Dopamine



Oxidants, Antioxidants And Neuroprotection

Pekka Rauhalä, Anya M.-Y. Lin, C.C. Chiueh, 1998

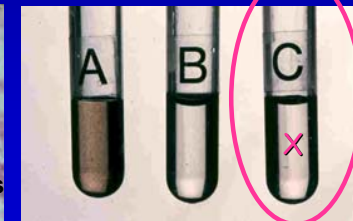
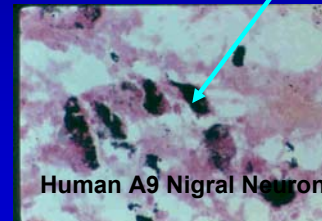
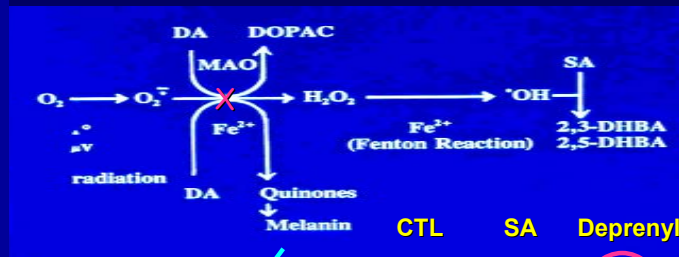
GSNO protects against iron-induced oxidative stress and nigrostriatal degeneration of brain A9 DA neurons in vivo

I-125 β -CIT
DAT brain imaging

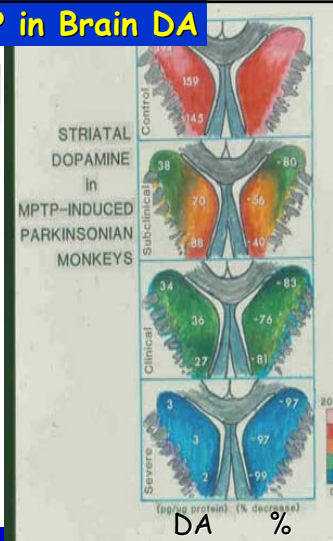
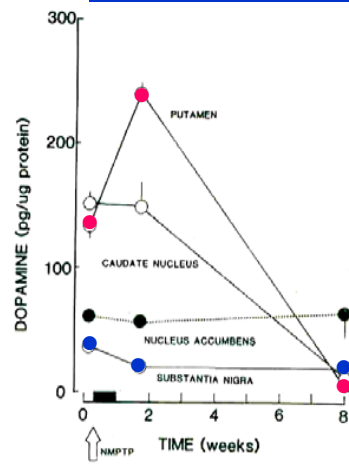
Possible Non-MAO-B Propargyl Effect

Selegiline Prevents Dopamine Auto-oxidation and Formation of Free Radicals and Melanin

Neuromelanin Formation in vivo & in vitro



Effects of MPTP in Brain DA



MPTP-induced Neurotoxicity

- MPP+: the toxic metabolite
- Selective degeneration of A9 nigral neurons greater than A10 mesolimbic neurons
- Species differences
 - Human/monkey >> dog >> rodent

The First MPTP-induced Monkey Model

Stan Burns,
C.C. Chiueh,
Sandy Markey
et al., PNAS, 1983



Dopamine Replacement Therapy

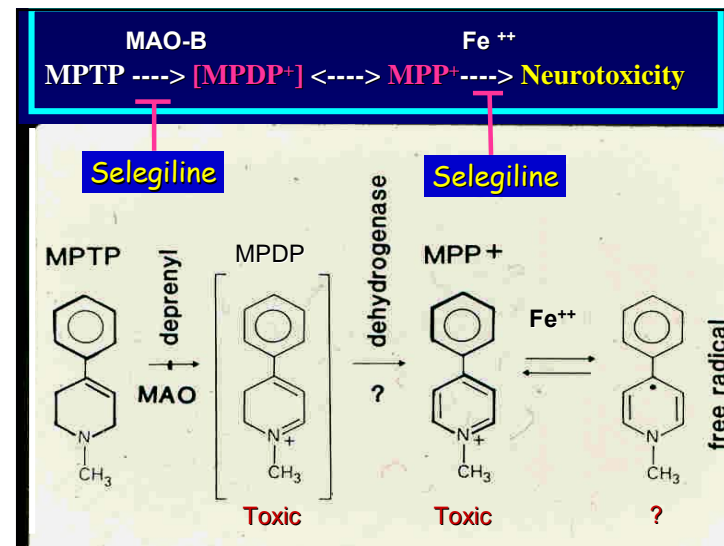


L-DOPA + CarbiDOPA

Old MAO-B Project of Selegiline

- ↓ Neurotoxicity caused by MPTP in monkey model
- Prevention the oxidation of MPTP to toxic MPP+

Stan Burns, Jon Johannessen, Sandy Markey,
Mike C.C. Chiueh (NIMH)



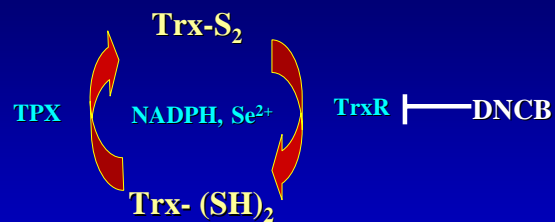
New Project of Selegiline

- Protect Against MPP⁺ in vivo, in vitro
Ruey-Meei Wu, (NTU Hospital, Neurology Dept)
Dennis L. Murphy (NIMH, Lab of Clinical Sci)
- New Mechanism: Induction of Thioredoxin
Tsugunobu Andoh (Toyama Med. Pharma. Univ)
 - Independent of MAO-B inhibition
 - Mimics preconditioning neuroprotection
 - Mediated by induction of survival proteins (Trx, MnSOD, Bcl-2)

Anti-oxidative Defense System

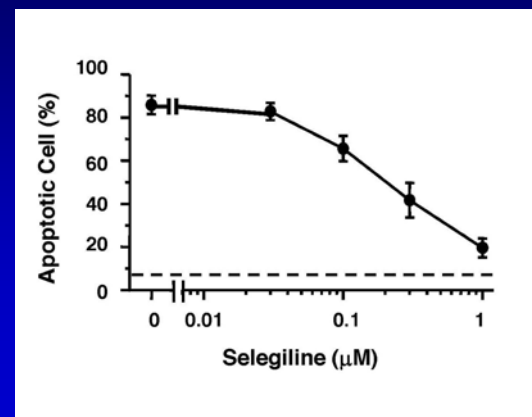
- Thioredoxin (Trx1; Trx2; Trx3)
- Glutaredoxin, Peroxiredoxin
- GSNO
- NO
- GSH (impermeable)
- MnSOD, CuZnSOD, catalase
- Vitamins: E (lipid-soluble), C (water-soluble)

Thioredoxin: A Redox Protein

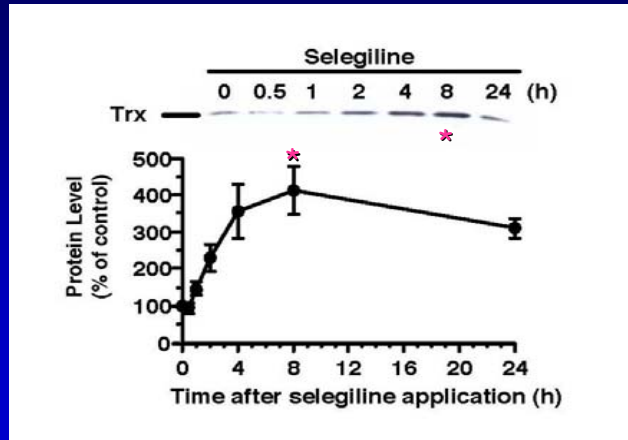


Subtypes: Trx-1, Trx-2, SpTrx
Active sites: (-Cys³²-Gly-Pro-Cys³⁵-)
Molecular weight: 12K

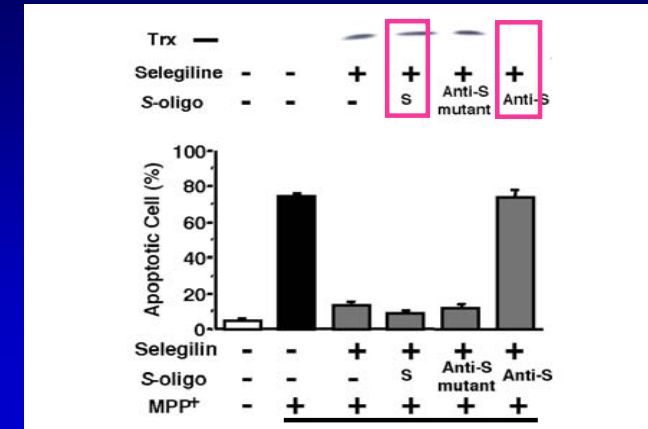
Selegiline Reduces MPP⁺-induced Apoptosis



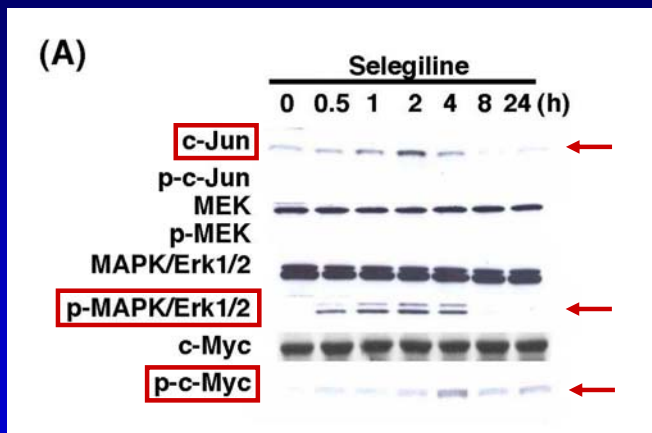
Induction of Thioredoxin (Trx) by Selegiline



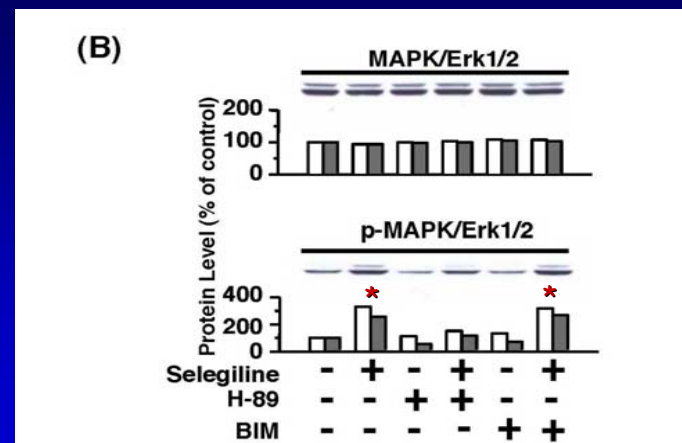
Role of Trx Expression in Selegiline's Action



Effects of Selegiline on cMyc Signaling

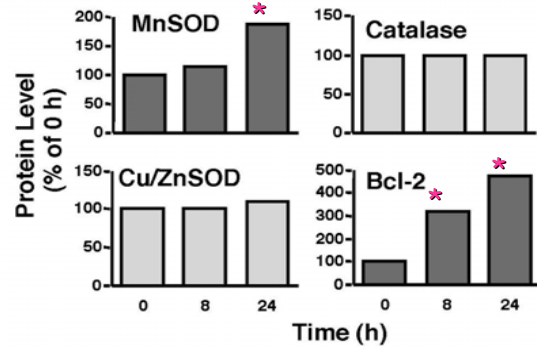


Up-regulation of p-MAPK via PKA Sensitive Pathway

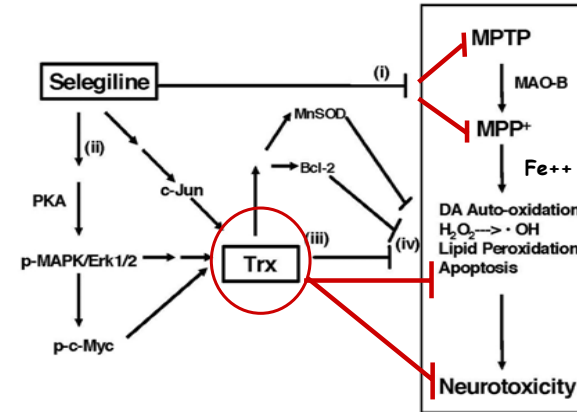


Selegiline Up-regulates MnSOD & Bcl-2

(A)



New Vista on Selegiline-induced Neuroprotection



Selegiline: New Mechanism of Action

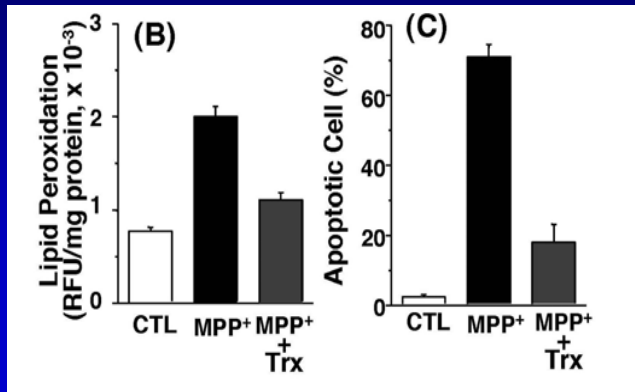
Mol. Pharmacol. , 68(5):1408-14, 2005
Andoh, Bloom, Murphy and Chiueh

- Not related to inhibition of MAO-B
- Induction of survival proteins
 - Trx Redox protein
 - Bcl-2 Anti-apoptosis
 - MnSOD Antioxidant

Trx: A Survival Protein

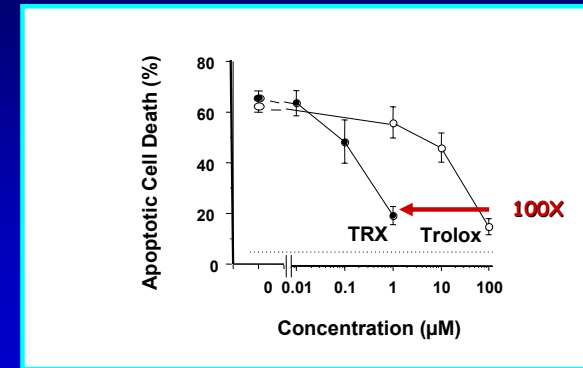
- Anti-oxidation
 Trx >> Vitamin E >> Vitamin C >> GSH
- Anti-inflammation
- Anti-apoptosis
- A redox active survival protein for tolerance or hormetic responses

Effects of Exogenously Administered Trx



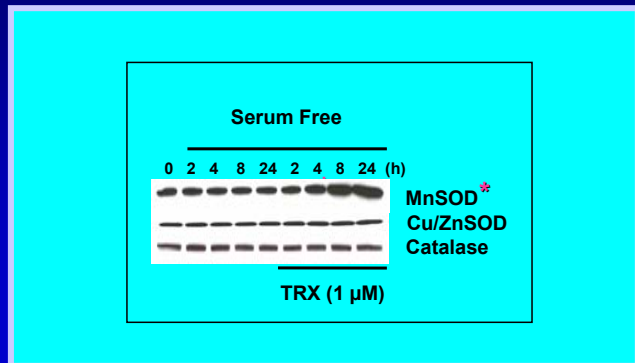
Trx: Antioxidation Potency

Trx >> Trolox >> GSH

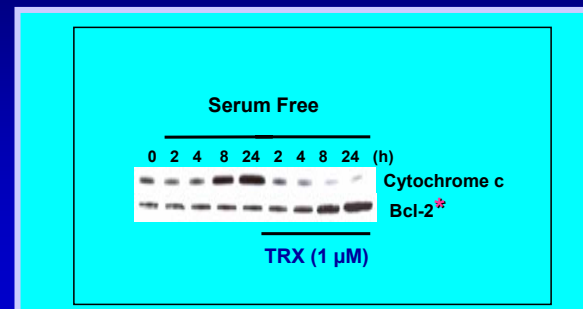


Trolox--Vitamin E analog

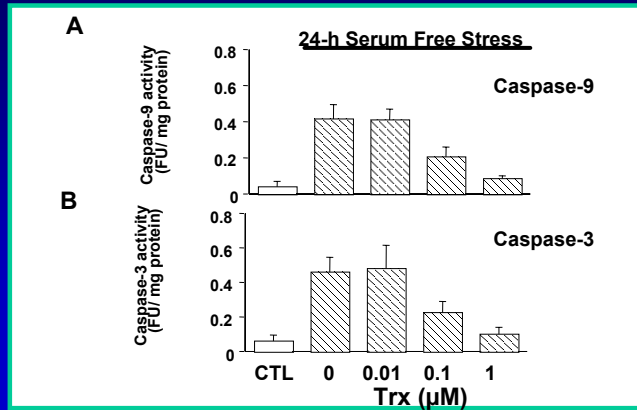
Effects of Trx on the Expression of MnSOD



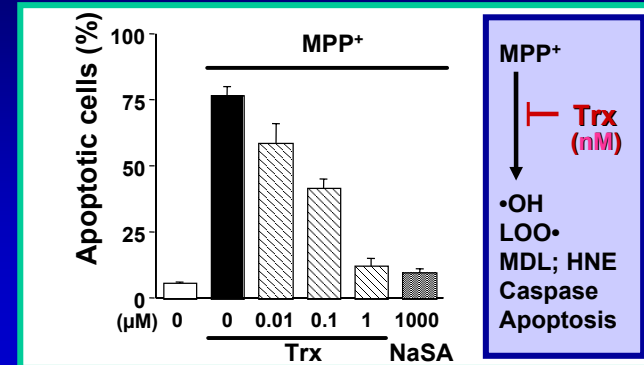
Effects of Trx on the Release of Mitochondrial Cytochrome c and the Expression of Bcl-2



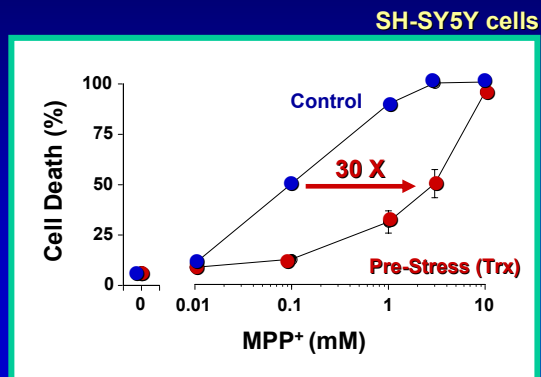
Effects of Trx on Caspases



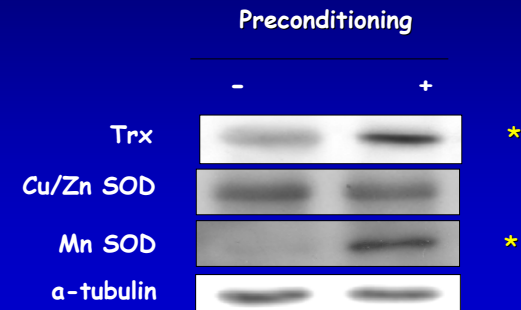
Effects of Thioredoxin (Trx) on Oxidative Stress and Neurotoxicity Caused by MPP⁺



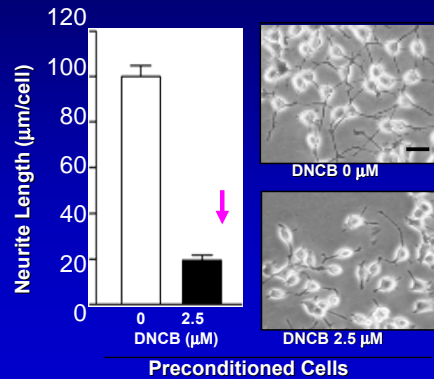
Endogenously Trx Mediates Preconditioning Tolerance Against MPP⁺



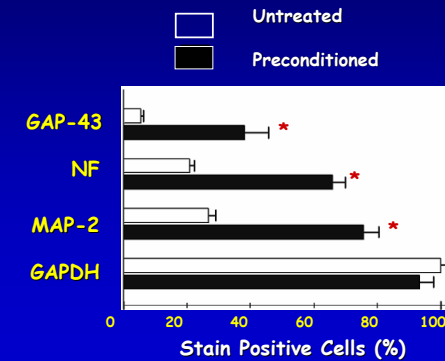
Induction of Trx in Preconditioned Cells



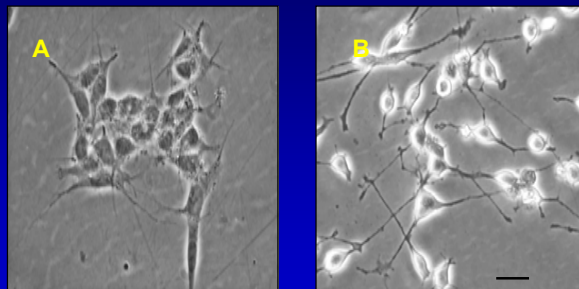
DCNB Inhibits Redox of Trx & Neurite Outgrowths



Induction of Neuron Specific Proteins



Chronic Preconditioning

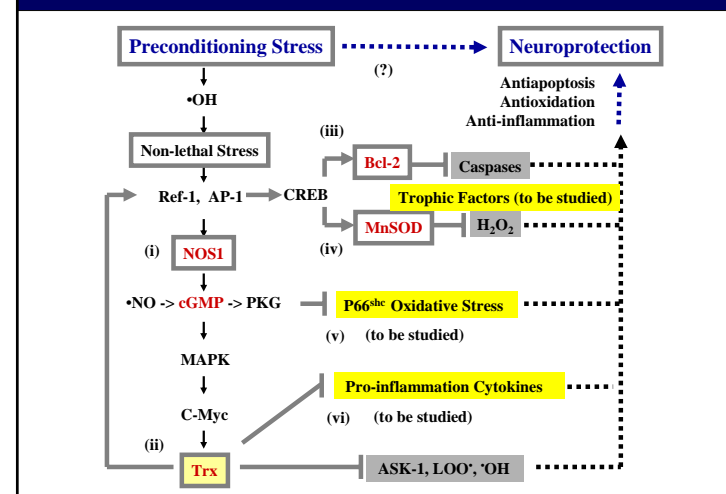


WT Untreated

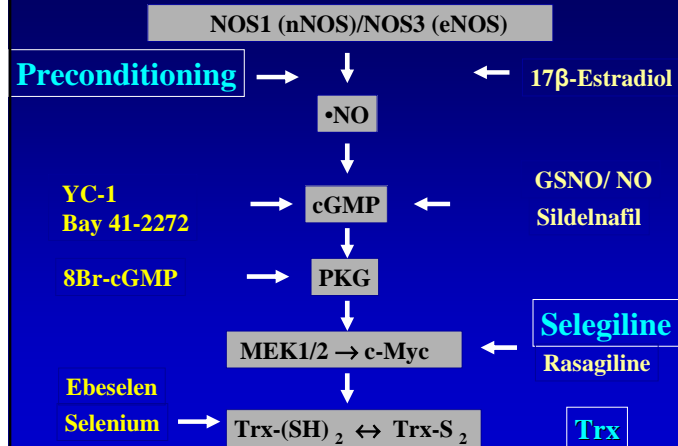
Preconditioned

Human SH-SY5Y Cells

Compensatory Defense Mechanism for Hormesis



R & D of New Trx-based Therapeutics



Conclusion

Selegiline: New Mechanism of Actions

1. Independent of MAO-B inhibition
2. Mimics preconditioning neuroprotection
3. Mediated by induction of survival proteins such as Trx
4. New indications:
Selegiline (Mike Chiueh)
Rasagiline (John Finberg; Moussa Youdim)

Targeted Therapy Based on Trx

- **Multiple Organ Failure**
 - Cardioprotection
 - Renal Failure
 - Acute Respiratory Distress Syndrome, API
- **Neuroprotection Against Neurodegeneration**
 - MPP+
 - Iron Complexes
 - Ischemic Oxidative Stress

Take Home Message

- Awakening the compensatory Trx defense system in the brain

