Neuroprotection in Parkinson's Disease

Graham A. Glass, MD

Assistant Professor of Neurology
University of California San Francisco

San Francisco VA Medical Center
Parkinson's Disease Research, Education and Clinical Center
(PADRECC)

Parkinson's Disease
Research,
Education &
Clinical Center
San Francisco VA
PADRECC

Current Therapy in PD

- Parkinson's Disease is one of the only "neurodegenerative" diseases in which medications alleviate symptoms
- The advent of carbidopa/levodopa significantly altered longevity in PD patients
- DBS therapy has allowed improved management in a number of patients
- Many years into PD, motor symptoms take a back seat to other problems, and we are more limited in therapies for these problems.

Levodopa Extends Lifespan

- Comparison of longevity in pre- and post-levodopa treatment patients revealed that patients treated with levodopa had less excess mortality than non-levodopa treated patients

Table 6. Comparison of Age and Duration of Illness at Death between Pre- and Post-levodopa Series of Patients

	Number of Patients	Number of Deaths	Age at Death, *yrs.*		Duration of Illness	
			Mean	Range	Mean	Range
Pre-levodopa (13)	802	340	65.9	38-91	10.8	1-41
Post-levodopa (present series)	100	32	73.1	63-90	12.1	3-28

Sweet et al., Ann Int Med 1975:83;456-463

Table 2 *Progression of disability in IPD: latencies to reach successive H+Y stages*

Study	HY 1	HY 2	HY 3	HY 4	HY 5
Pre-levodopa					
Hoehn + Yahr, 1967	3.0	6.0	7.0	9.0	14.0
Marttila + Rinne, 1977	—	2.9	5.5	7.5	9.7
Post-levodopa					
Hoehn, 1983	—	9.0	12.0	12.0	18.0
Hely et al., 1999	—	—	4.0	7.0	6.0
Müller et al., 2000	—	3.0	5.5	14.0	15.0
Lücking et al., 2000	—	11.0	19.0	26.0	40.0

Poewe, W. Neurology 2006;66:S2-S9

Table Predominant problems among surviving subjects at 15 years of follow-up

	Percent of subjects experiencing
Neuropsychiatric	
Cognitive decline	84
Dementia	48
Daytime sleepiness	79
Depression (mostly mild)	50
Hallucinations	21
Axial motor	
Falls	81
Fractures	23
Dysphagia	50
Severe dysarthria	27
Autonomic	
Urinary incontinence	41
Symptomatic postural hypotension	35

As reported by Hely et al.[29]

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Marras, C. et al. Neurology 2008;70:1996-2003

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What are people doing to slow down PD?

- Other therapies further treat symptoms.
- Some are thought to be neuroprotective and efforts are being made to prove this (selegiline, rasagiline, Mirapex and Mirapex LA
- Tons of studies as seen below…..but.

TABLE 1. *Randomized trials of neuroprotective agents in Parkinson's disease*[a]

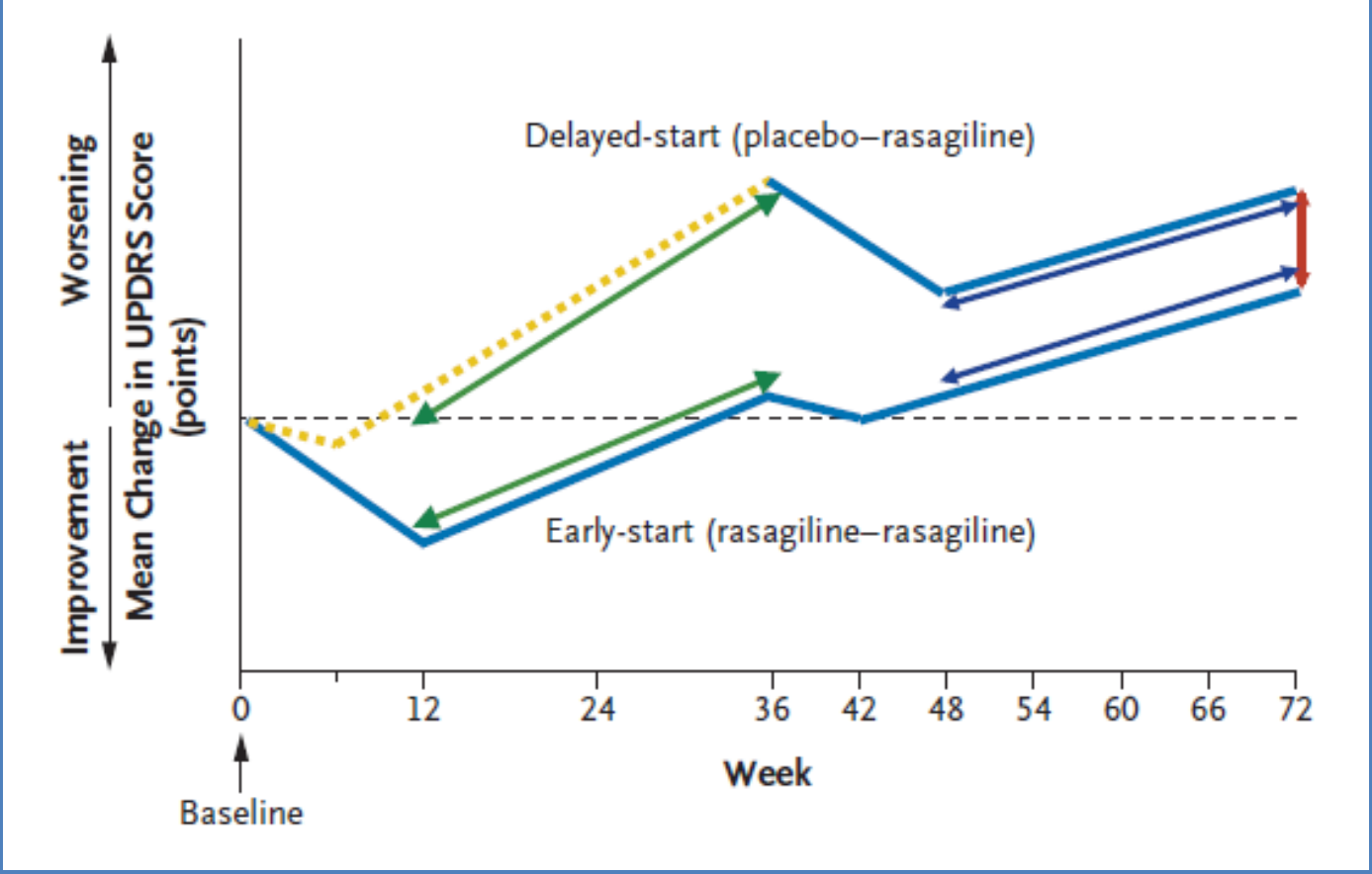
Trials	Active agents	Putative mechanisms	N	Primary outcomes*
Completed, Published Trials				
1. Tetrud and Langston[15]	selegiline	antioxidant/anti-apoptotic	54	Time to levodopa Rx
2. DATATOP[4]	selegiline and tocopherol	antioxidant/anti-apoptotic	800	Time to levodopa Rx
3. SINDEPAR[16]	selegiline[b]	antioxidant/anti-apoptotic	101	Change in UPDRS
4. ROADS[17]	lazabemide (4 dosages)	antioxidant/anti-apoptotic	321	Time to levodopa Rx
5. Swedish Selegiline[18]	selegiline	antioxidant/anti-apoptotic	157	Time to levodopa Rx
6. Norwegian-Danish[19]	selegiline	antioxidant/anti-apoptotic	163	Change in UPDRS
7. QE2[20]	coenzyme Q10 (3 dosages)	antioxidant/mitochondrial stabilizer	80	Change in UPDRS
8. Jankovic and Hunter[21]	riluzole	NMDA antagonist	20	Change in UPDRS
9. TEMPO[22]	rasagiline (2 dosages)	antioxidant/anti-apoptotic	404	Change in UPDRS
10. ELLDOPA[5]	levodopa (3 dosages)	dopaminergic	361	Change in UPDRS
11. U.K. Low-dose Pergolide[23]	pergolide	antioxidant	106	Time to levodopa Rx
12. NET-PD futility #1[24]	minocycline, creatine	anti-inflammatory, mitochondrial stabilizer	200	Change in UPDRS
13. TCH346[25]	TCH346 (3 dosages)	anti-apoptotic	301	Time to dopaminergic Rx
14. NET-PD futility #2[26]	GPI-1485, coenzyme Q10	trophic factor antioxidant, mitochondrial stabilizer	213	Change in UPDRS
15. PRECEPT[27]	CEP-1347 (3 dosages)	anti-apoptotic	806	Time to dopaminergic Rx
Ongoing or Unpublished Trials				
16. NIL-A[c] (completed 2002)	GPI-1485 (2 dosages)	trophic factor	300	Change in UPDRS motor
17. Riluzole[c] (completed 2002)	riluzole (2 dosages)	NMDA antagonist	1084	Time to dopaminergic Rx
18. Guilford GPI-1485[d] (completed 2006)	GPI-1485	trophic factor	~200	Change in UPDRS
19. MitoQ trial[e] (completed 2007)	mitoquinone (2 dosages)	mitochondrial antioxidant	120	Change in UPDRS
20. QE3[f]	coenzyme Q10 (2 dosages)	antioxidant/mitochondrial stabilizer	600	Change in UPDRS
21. ADAGIO[g] (completed 2008)	rasagiline (2 dosages)	antioxidant/anti-apoptotic	1176	Change in UPDRS
22. NET-PD LS Creatine[h]	creatine	mitochondrial stabilizer	1720	Global statistic
23. PROUD[i]	pramipexole	dopaminergic	535	Not reported

ADAGIO Trial

- Delayed-start design with four arms, either early or delayed administration of two doses (1mg, 2mg) of rasagiline
- 1,146 subjects vs. 404 in TEMPO trial
- 9 months for both arms of study vs. 6 months in TEMPO
- 3 Endpoints vs. 1 in TEMPO

Olanow et al., NEJM 2009;361:1268-78

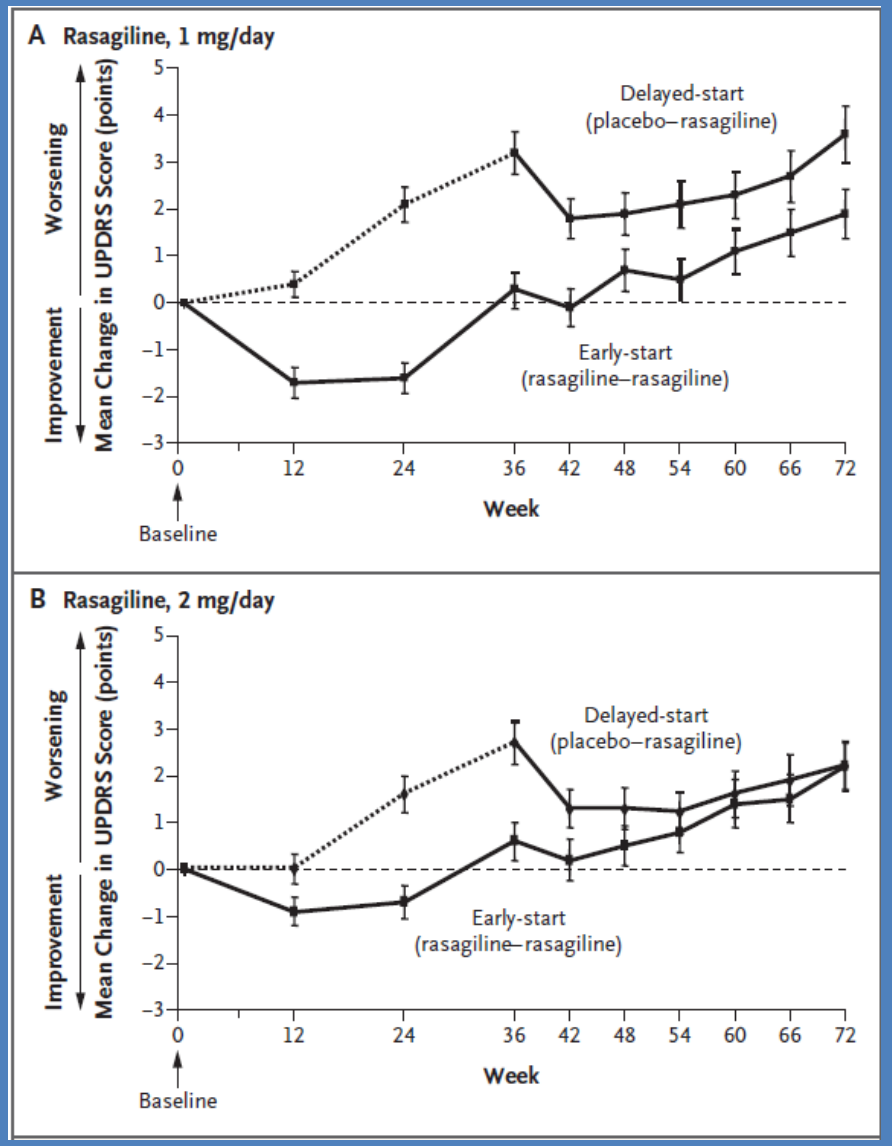
ADAGIO Endpoints



Olanow et al., NEJM 2009;361:1268-78

ADAGIO Trial Results

- 1mg dose met all 3 endpoints
  - Baseline to end change in UPDRS
  - Slope of curves in weeks 12-36
  - Non-inferiority in slope of weeks 48 to 72
- 2mg dose met none



Problems with Interpretation of ADAGIO

- Possibly biased sample due to selection of patients likely to 'survive' placebo phase of study
- Using UPDRS, especially 'old' UPDRS has problems
  - Not very sensitive to early changes in symptoms
  - Subjective
  - Likely not linear progression
- Difference between early and delayed start groups (about 2 UPDRS total points) was only about 1% of total
- Failure or 2mg dose to meet any endpoints

Adapted from Ahlskog and Uitti *Neurology 2010;74;1143-1148*

Why didn't 2mg work?

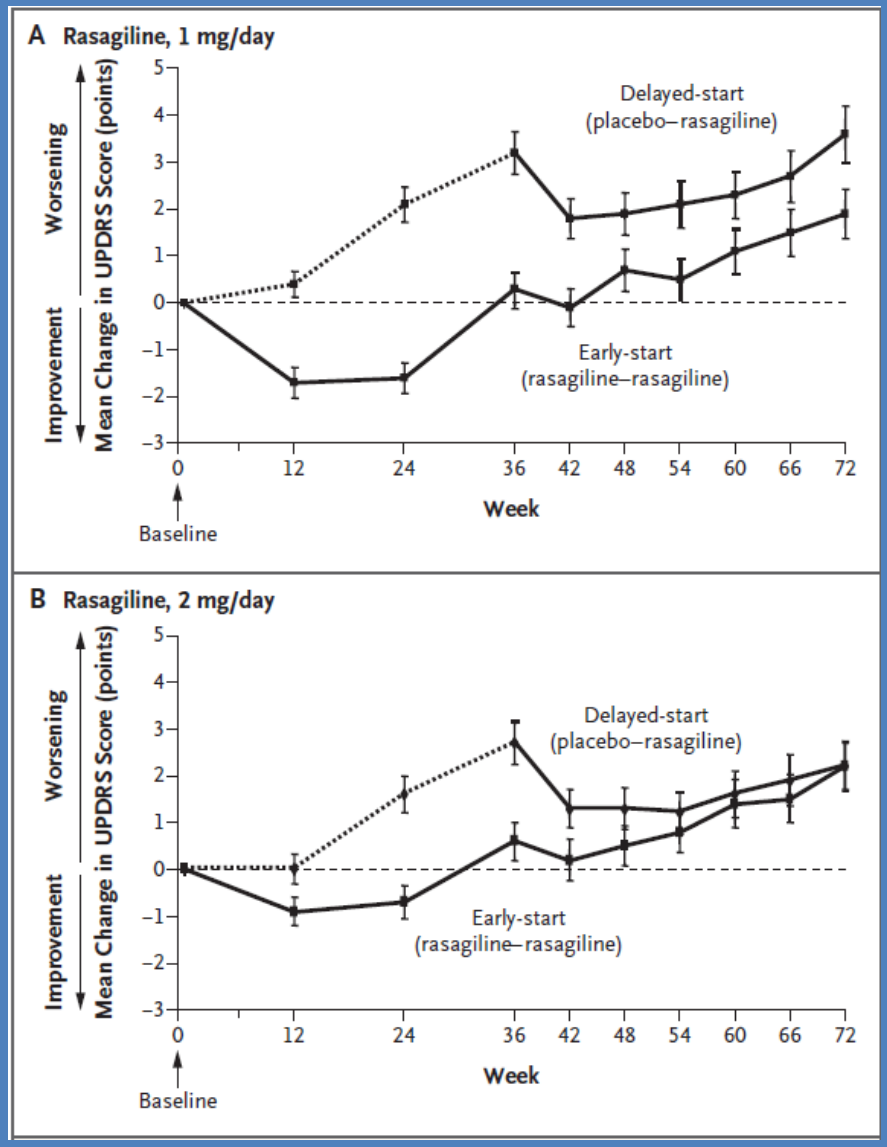
- Possible Explanations
  - Symptomatic benefit masked disease-modifying effect
    - But, symptomatic effect was equal between doses in first phase
    - MAO-B nearly completely inhibited at both doses
  - Disease modifying effect may be independent of MAO-B inhibition and more potent at lower doses
    - But propargylamine compound TCH346 failed in large Trial

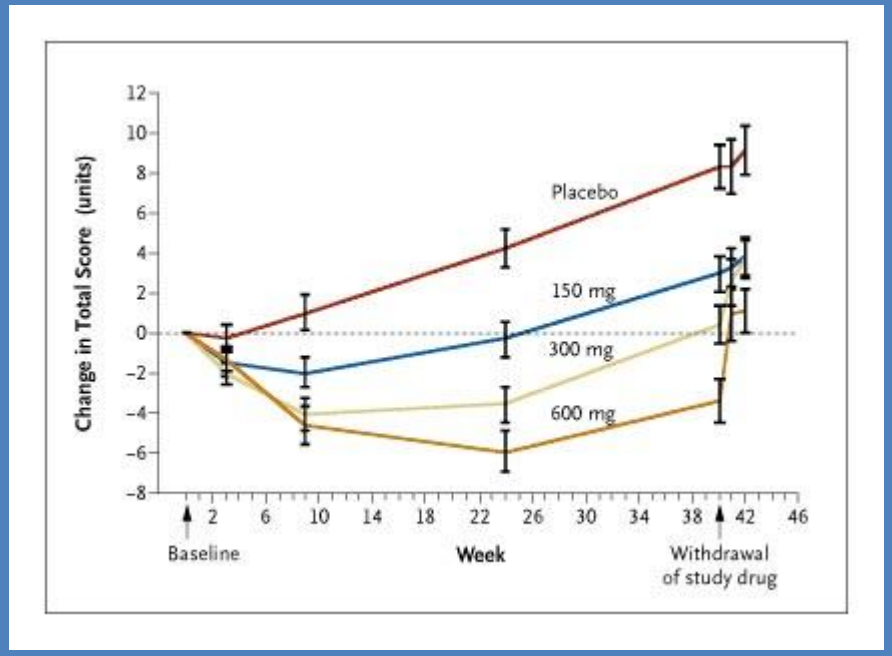
Other Problems

- Variability in response to rasagiline was twice the magnitude of the positive finding of the study:
  - Delayed-start, active phase 2mg +1.16 pts
  - Delayed-start, active phase 1mg -0.23
  - Early-start, first phase 2mg -1.11
  - Early-start, first phase 1mg -1.26
  - Early-start, second phase 1mg -1.56
  - Early-start, second phase 2mg -2.36

  Range 3.52 pts
- Design assumed that symptomatic effect would plateau by 12 weeks, but this does not seem to be the case
- Does rasagiline even do better than levodopa?

Adagio vs. Elldopa





Fahn et al. NEJM 2004;351: 2498-508

I can't get no satisfaction

Still no neuroprotection for Parkinson disease

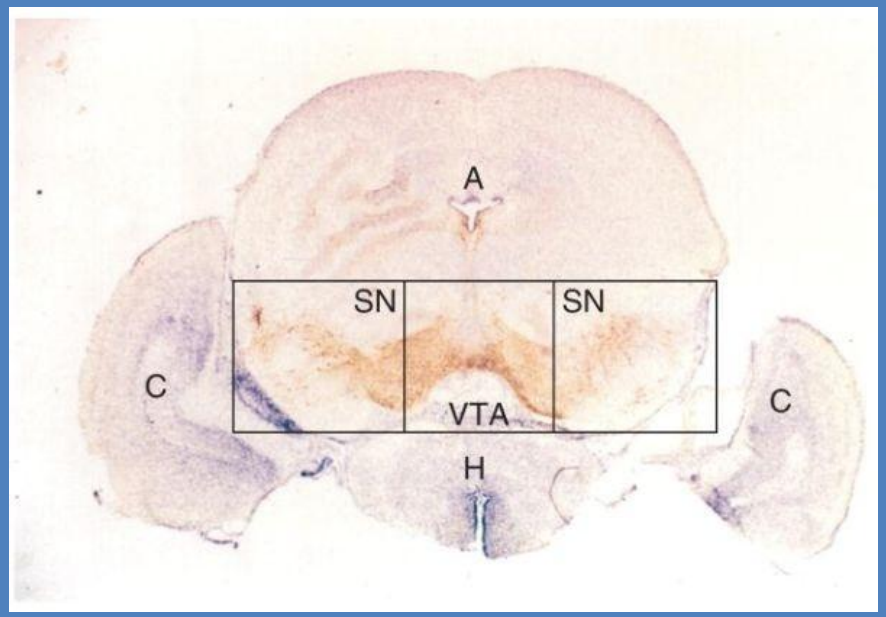
- Editorial written following PSG Trial based on CEP-1347, an anti-apoptotic therapy in PD
- 2 points made in this editorial
  - ?Animal Models for PD
  - ?simplification of apoptosis vs. necrosis of cells

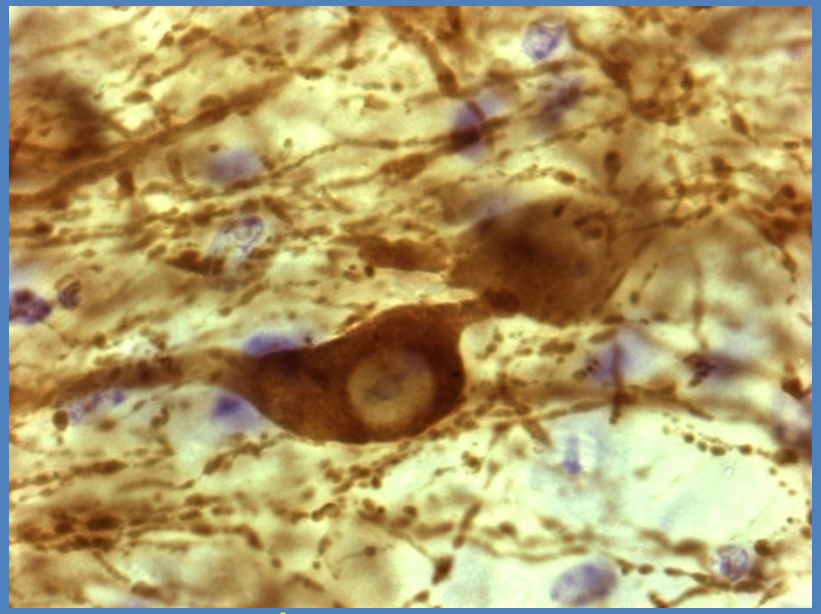
J. Eric Ahlskog
Neurology 2007;69:1476-1477

Back to the Drawing Board!

- What are we protecting from?
- Retrospective thinking
- Faulty logic based on grossly incomplete models of PD
- Measurements of PD progression very limited
- Inability to “screen” good compounds based on poor animal models

Of Mice and Men





- Mouse substantia not nigra – not pigmented
- Equal over-expression of α-synuclein does not lead to aggregation/ neuronal demise in mice
- Mouse lifespan much shorter – most studies ignore effects of aging
- A53T α-synuclein mutation in humans is normal sequence in mouse

Does everyone with “pre-clinical” PD end up getting PD?

Incidental Lewy Body Disease and Preclinical Parkinson Disease

Anthony DelleDonne, PhD; Kevin J. Klos, MD; Hiroshige Fujishiro, MD, PhD; Zeshan Ahmed, BSc
Joseph E. Parisi, MD; Keith A. Josephs, MD, MST; Roberta Frigerio, MD; Melinda Burnett, MD;
Zbigniew K. Wszolek, MD; Ryan J. Uitti, MD; J. Eric Ahlskog, PhD, MD; Dennis W. Dickson, MD

- 8-17% of patients who pass away without ever having a PD symptom are discovered to have “pre-clinical PD
- iLB’s are found in various tissues in the nervous system.

Parkinson's as we think about it now

Olanow, C. W. et al. Neurology 2009;72:S1-S136

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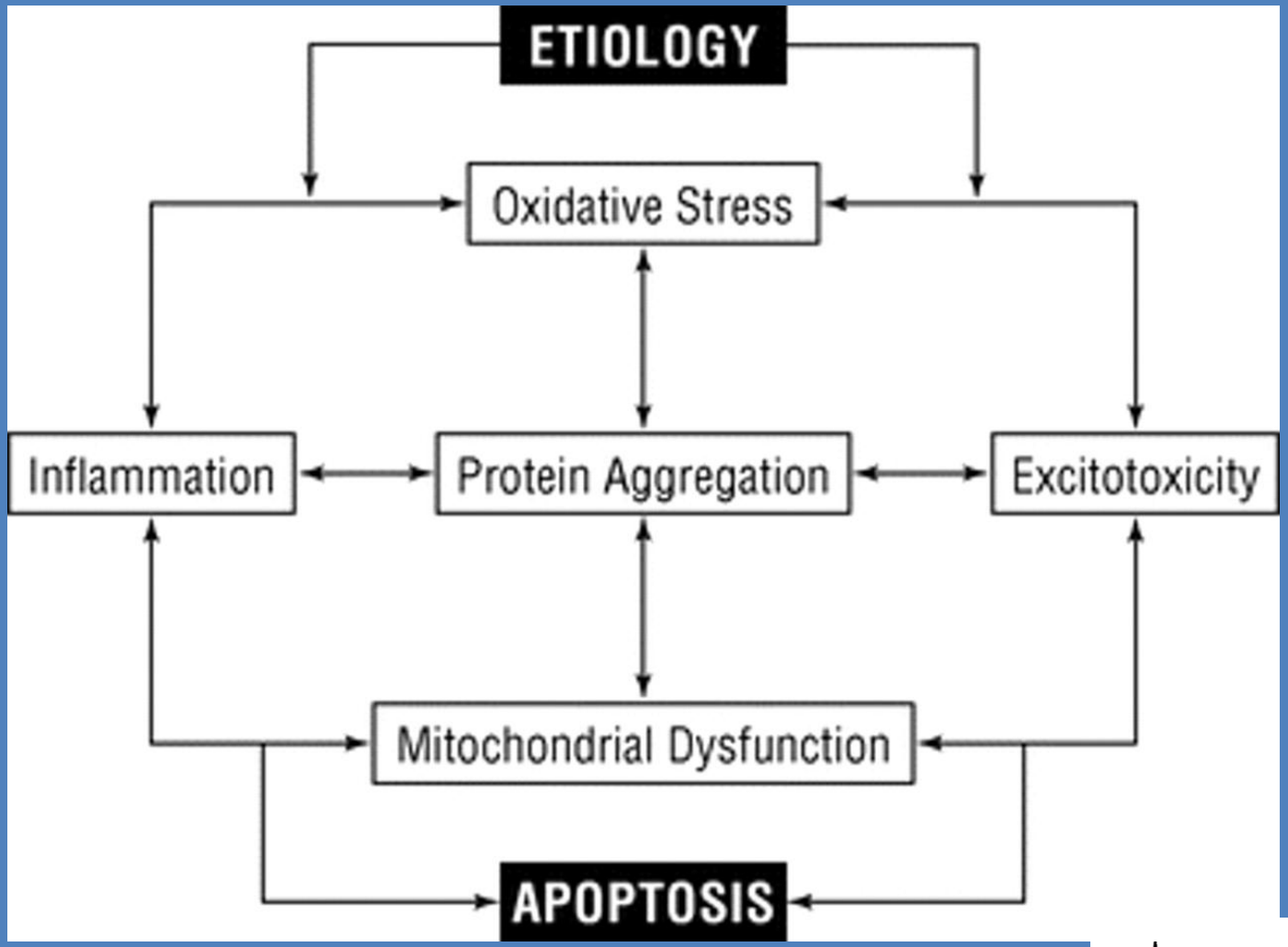
Parkinson's as a Multi-system Disease

Langston, 2006

What triggers PD Pathology?



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Olanow, C. W. et al. Neurology 2009;72:S1-S136

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Glutathione in PD

- GSH is the most abundant antioxidant in the brain and is selectively reduced in PD
- The magnitude of glutathione depletion correlates with severity of PD
- Earliest indicator of nigral degeneration
- Not decreased in other atypical parkinsonian syndromes

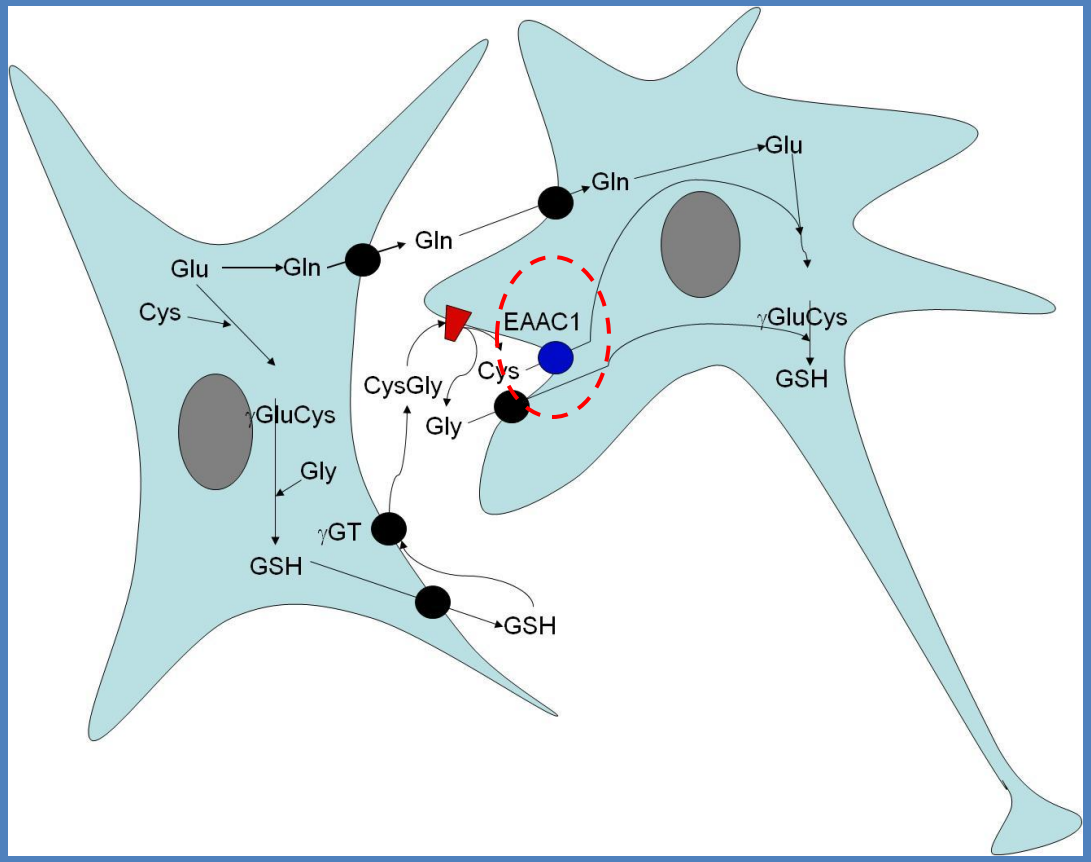
Glutathione Role in PD

- Removes reactive oxygen and nitrogen species
- Depletion results in reduced DA content, increased lipofuscin deposition and increased numbers of dystrophic axons in dopaminergic fibers, mitochondrial damage
- Glutathione levels cannot be restored by direct supplementation because glutathione crosses the blood brain barrier via a saturatable mechanism and is not taken up by neurons

Neuronal GSH synthesis:

- cysteine availability is rate-limiting for GSH synthesis
-most cell types obtain Cys-Cys (cystine) from the extracellular space, rather than free cysteine.
-but mature CNS neurons are different; neurons take up free cysteine itself, indirectly provided by astrocytes

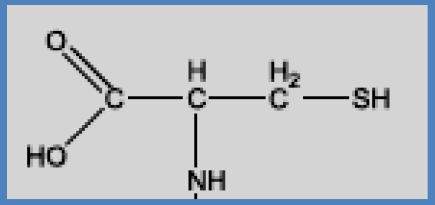
GSH = glu-cys-gly



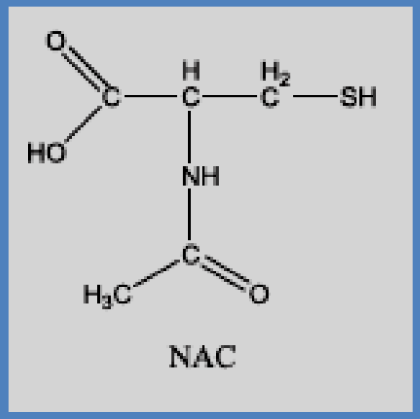
NAC

- Cell permeable precursor of cysteine that crosses the BBB, enters neurons and is capable of restoring GSH in a concentration dependent fashion
- Oral bioavailability is 9.1%
- NAC crosses mice BBB at 2.4L/g-min which is comparable to many centrally active peptides
- Already in clinical use

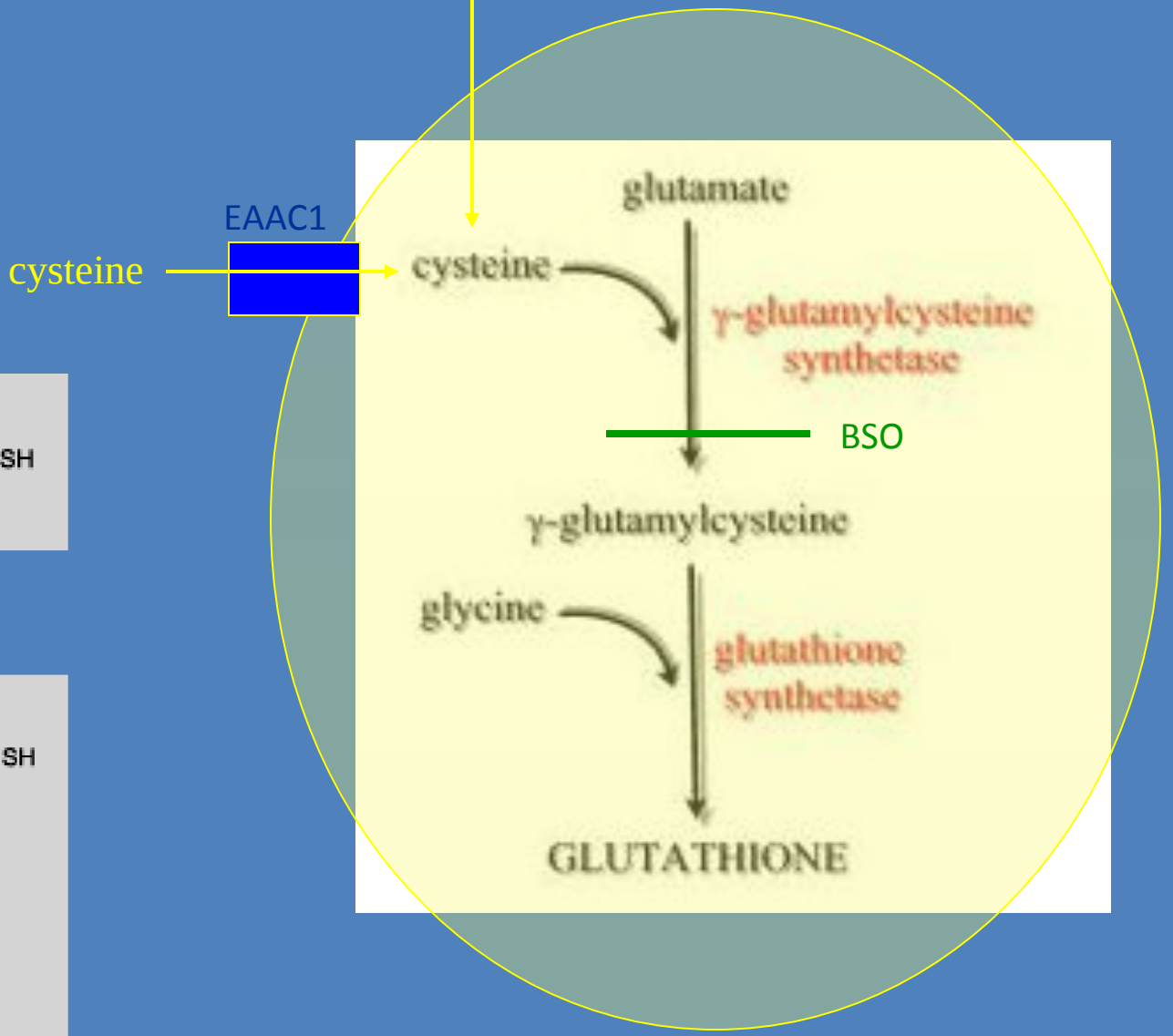
NAC is a membrane-permeable cysteine precursor



Cysteine



NAC



Animal Data

- Two studies have shown that NAC is protective from MPTP-ism.
- Mice deficient in EAAC1 were shown to have decreased neuronal GSH content, increased neuronal oxidative stress, and widespread age-dependent neuronal loss. These mice showed a 42% loss of SN dopaminergic neurons over one year of life.

EAAC1 was originally classified as a glutamate transporter

Na^+ - dependent, concentrative Excitatory Amino Acid Transporters:

EAAT1 = GLAST - astrocyte specific
EAAT2 = GLT1 - astrocyte specific
EAAT3 = EAAC1 - neuron specific
EAAT4
EAAT5

The large majority of glutamate uptake in brain is performed by astrocytes.

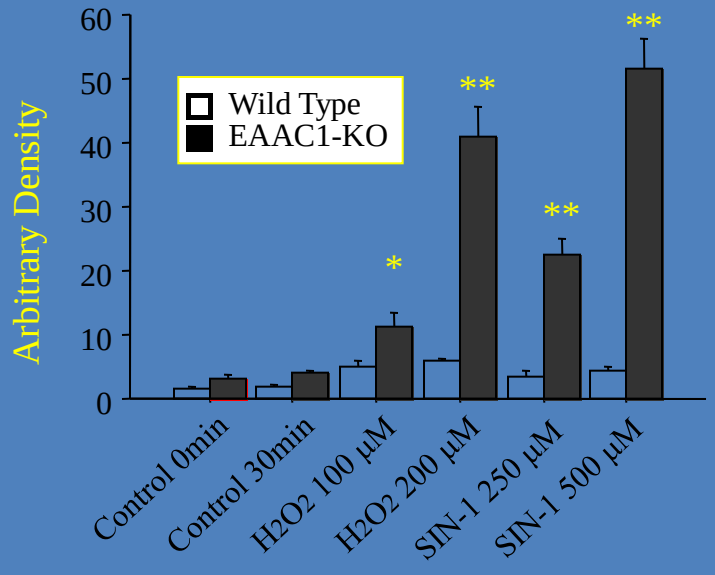
- Unlike the other EAATs, EAAC1 is not clustered around synapses, and it has a 10-fold greater affinity for cysteine than for glutamate, suggesting that cysteine uptake is its primary role

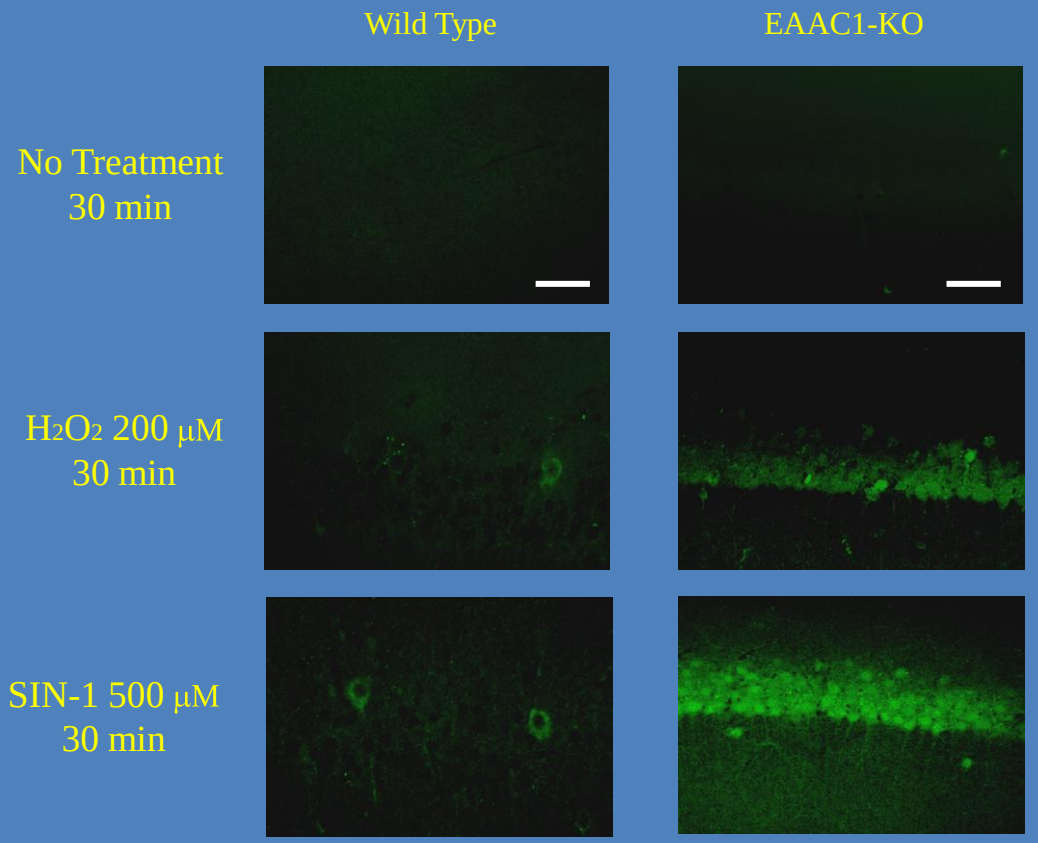
NAC protective

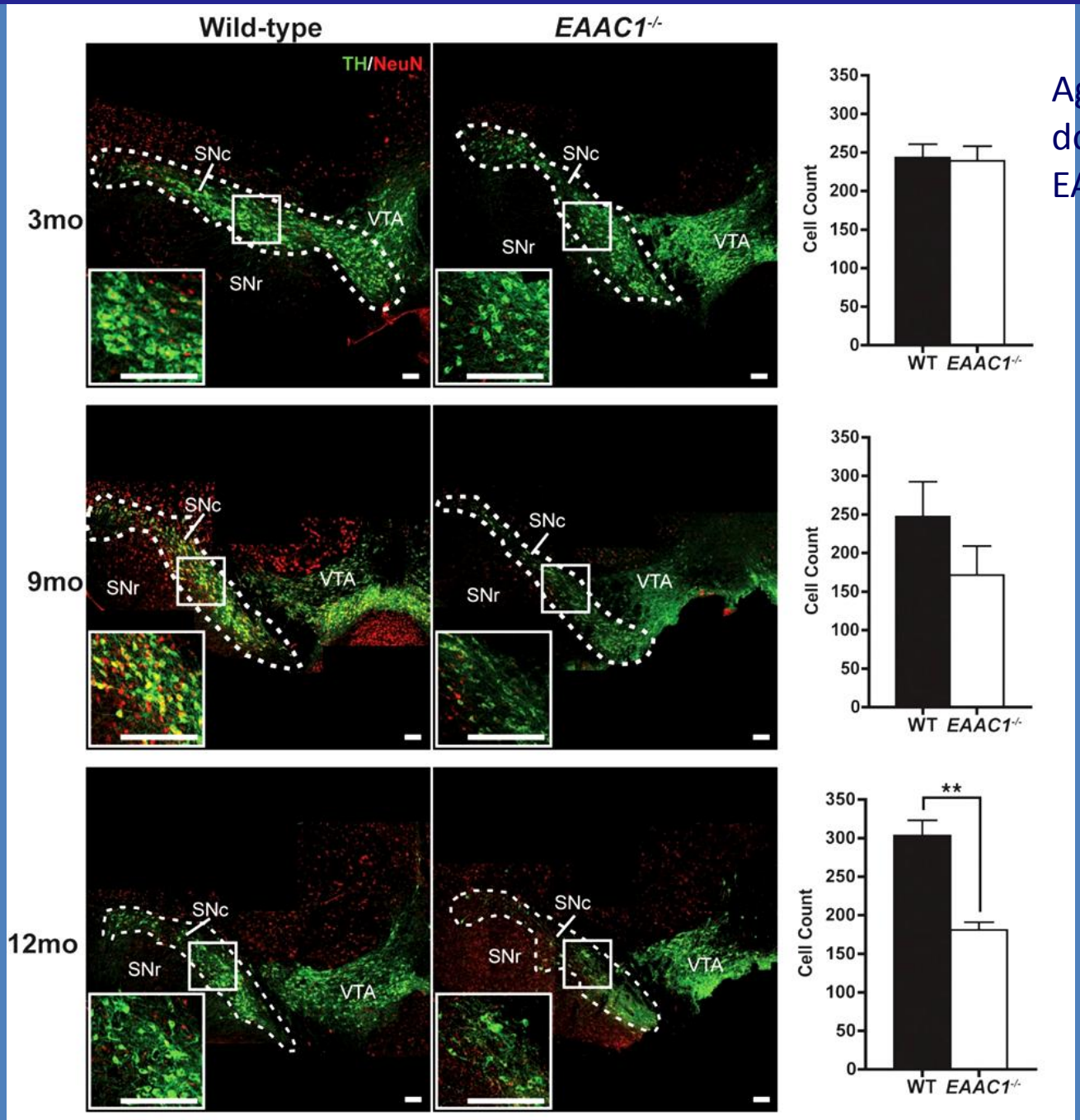
- When these mice were given oral NAC starting at age 3 weeks there was no loss of dopaminergic SNc neurons at age 12 months, reduced nitrotyrosine immunoreactivity in dopaminergic SNc neurons, and improved motor performance.

EAAC1$^{-/-}$ mouse brain slices:

Neurons show reduced capacity to scavenge ROS (DCF fluorescence)

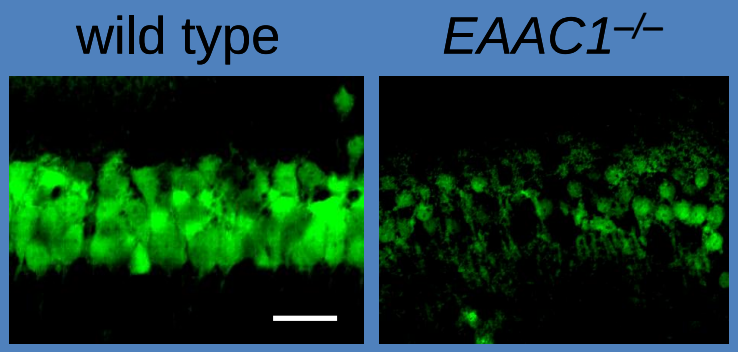




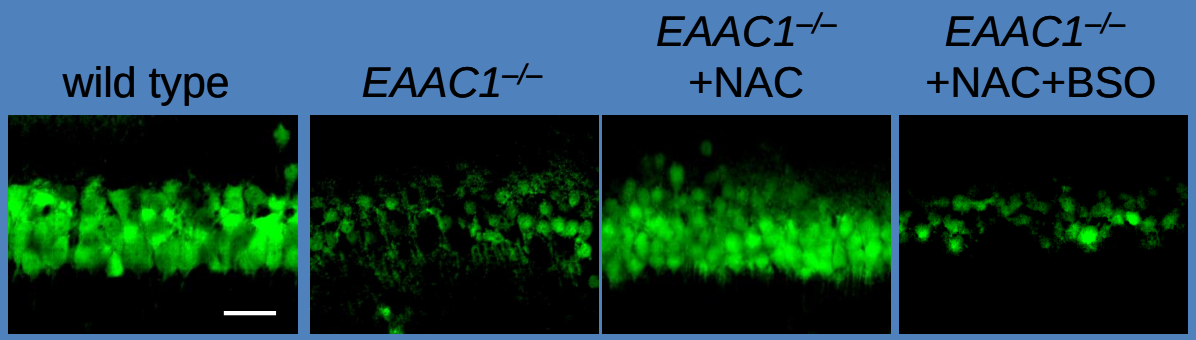


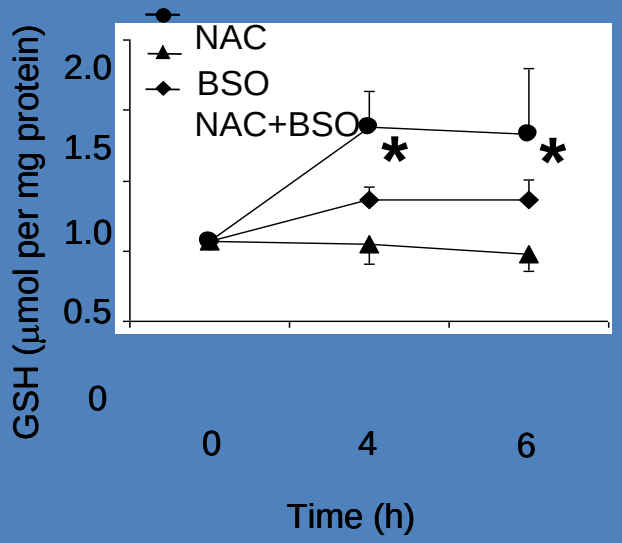
Age-dependent loss of SNc dopaminergic neurons in EAAC1$^{-/-}$ mice

Reduced GSH content in EAAC1$^{-/-}$ brain neurons
(C5-maleimide flourescence)

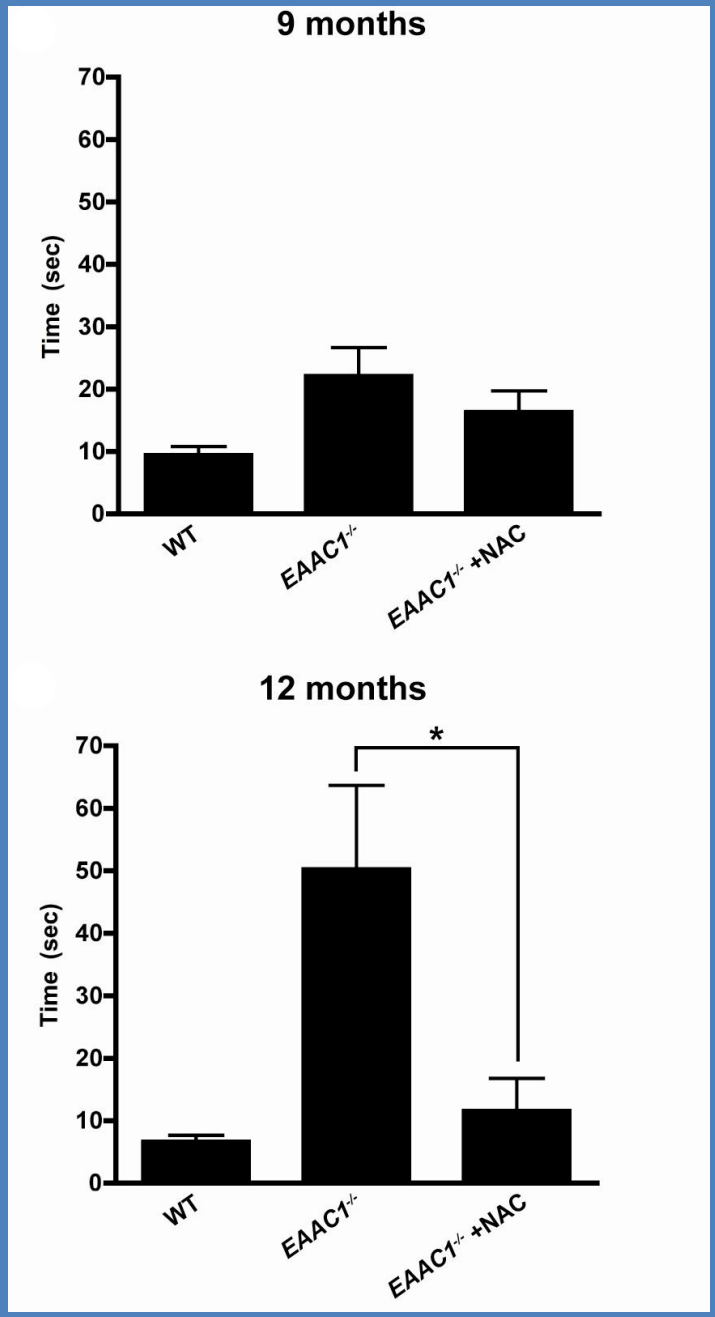


NAC restores GSH content in EAAC1$^{-/-}$ brain neurons





Pole test


9 months
Time (sec)
70
60
50
40
30
20
10
0
WT
EAAC1-/-
EAAC1-/- +NAC
12 months
*
Time (sec)
70
60
50
40
30
20
10
0
WT
EAAC1-/-
EAAC1-/- +NAC

CSF (data expressed as mean±SE)
* different from control

	Control	NAC	NACA	GSH	One way Anova P value
Cystine (CySS: μM)	0.67±0.13	1.01±0.06	1.34±0.15	2.41±0.48*	0.003
Cysteine (Cys: μM)	6.51±0.75	7.62±0.44	7.95±0.72	10.92±0.64*	0.003
CyS-GSH (μM)	1.30±0.31	1.05±0.26	1.18±0.26	2.15±0.51	0.160
GSH (μM)	6.15±0.31	5.95±0.24	4.77±0.18	9.81±1.33*	0.001
GSSG (μM)	1.71±0.56	1.26±0.19	1.16±0.13	2.75±0.53	0.059
Eh (GSSG/GSH)	-126.47±4.19	-127.93±2.74	-123.07±2.39	-130.38±3.06	0.455
Eh (CySS/Cys)	-123.92±0.56	-122.73±1.03	-120.13±1.19	-121.49±2.15	0.283
Total GSH	10.86±1.50	9.53±0.33	8.27±0.37	17.47±2.44*	0.003
Total Cys (μM)	9.19±1.28	10.69±0.73	11.82±1.15	17.89±1.37*	0.001

Why do we need to rethink design

- Traditional Double-Blind Placebo trials are too large and costly for questionable agents (Creatine/CoQ10).
- Delayed Start Trials are large, costly, and exclude the use of patients on therapy with other agents (ADAGIO n=1176)
- Traditional Futility designs often rely on historic control, still require large numbers of patients and result in needless replication

Placebo Calibrated??

- Futility designs have relied on historic progression rates to determine modulation
- Problematic if your group progresses more rapidly or slowly than “historic controls”
- Calibration of appropriate rate of progression to compare active agent to occurs such that if the estimated increase in UPDRS scores from baseline to 24 weeks in the calibration group falls outside the 95% CI for the projected rate of historic controls (CoQ10 vs Creatine)

Which Historic Controls

- ELLDOPA trial database is open via PSG
- Rate of Progression for 24 weeks in the 300mg and 600mg treated groups is 5.12 UPDRS points
- Re-Calibration occurs if the estimated increase in UPDRS scores from baseline to 24 weeks in the calibration group falls outside the 95% CI for the projected rate of ELLDOPA progression

Non-Superiority??

- Based on ELLDOPA data and recommendations by the NET-PD investigators a 30% reduction in progression (5.12 vs 3.58).
- Something of an arbitrary cut-off
- Historically, futility (non-superiority is needed to keep “n” low)—CoQ10, GPI-1485, placebo (71, 71,71)

Linear Mixed Models and Power??

- For repeated continuous outcomes
- Makes use of interim UPDRS measures at weeks 2, 4, 8, and 16
- Better for patients who do not complete the study (vs. “last observation carried fwd)
- Significantly improves power and deals more accurately with disease progression (9 mos Ahlskog argument)

Conclusions

- Identification of appropriate agents requires advances in animal models
- Assessment of promising agents requires advances in trial design
- NAC may represent an agent worthy of further evaluation


thank you
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Parkinson's Disease

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