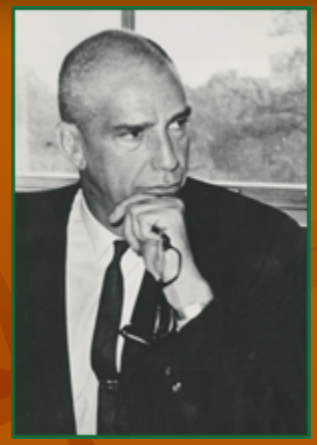


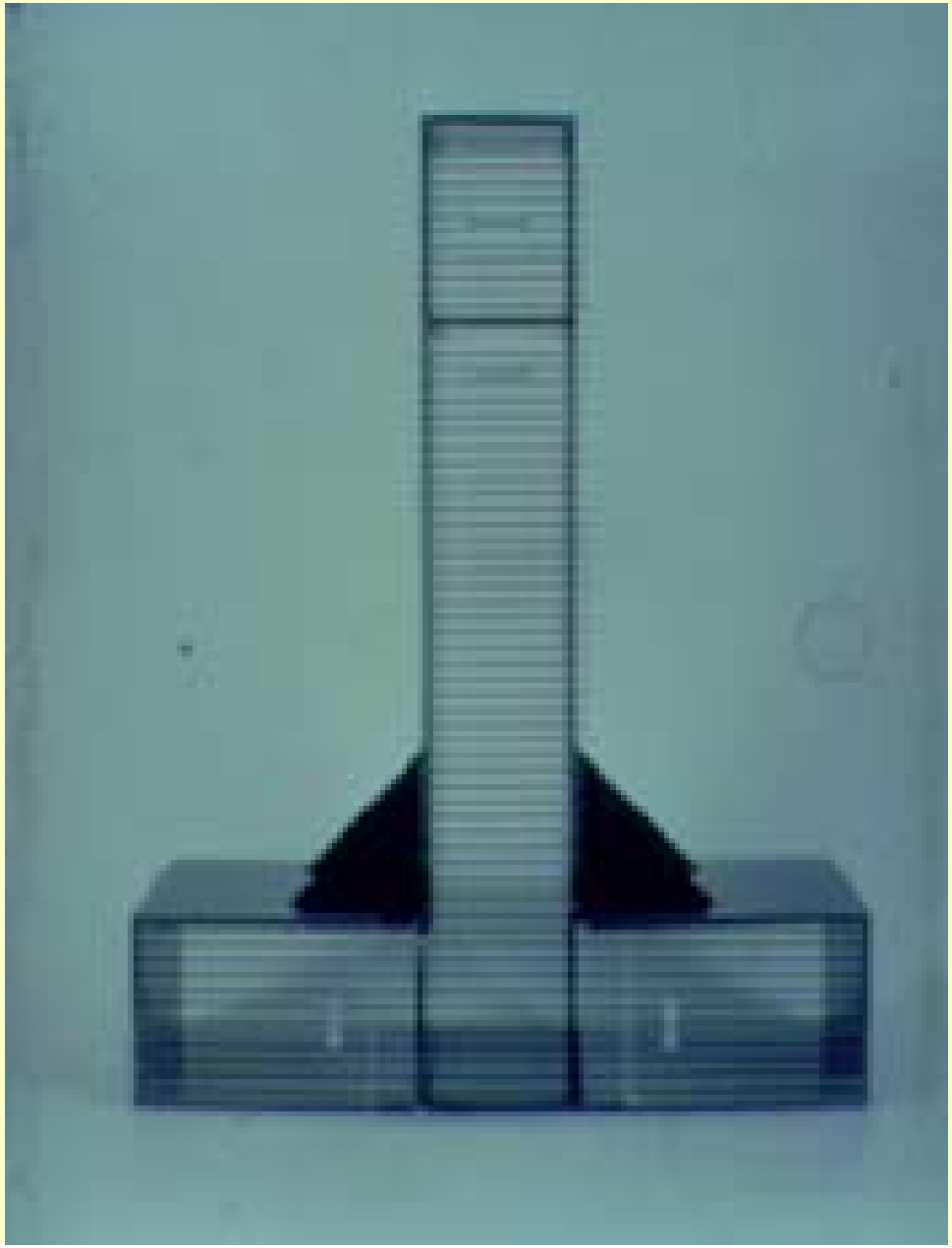
Hormesis and Memory

John E Morley

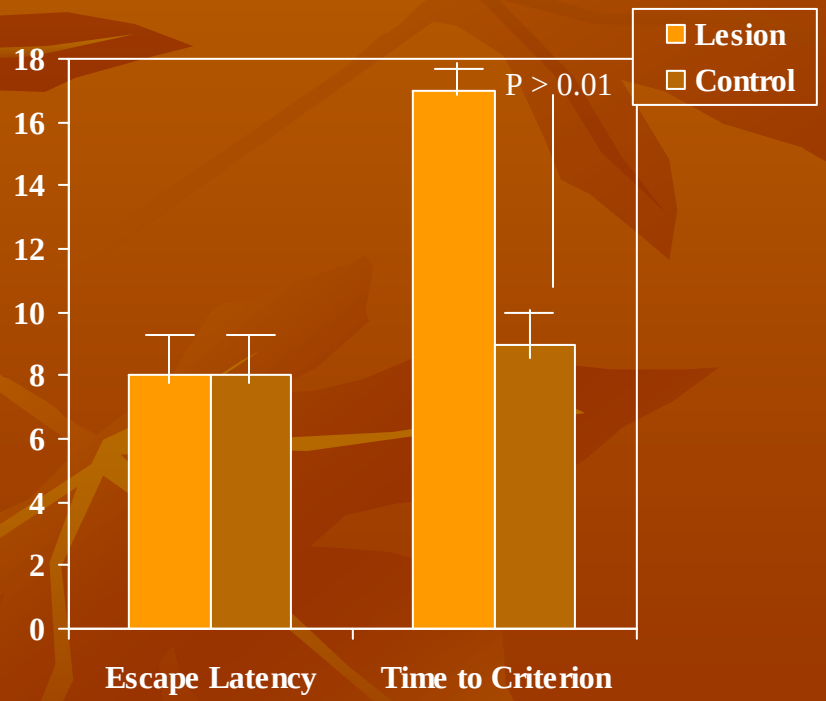
Geriatrics

Saint Louis University

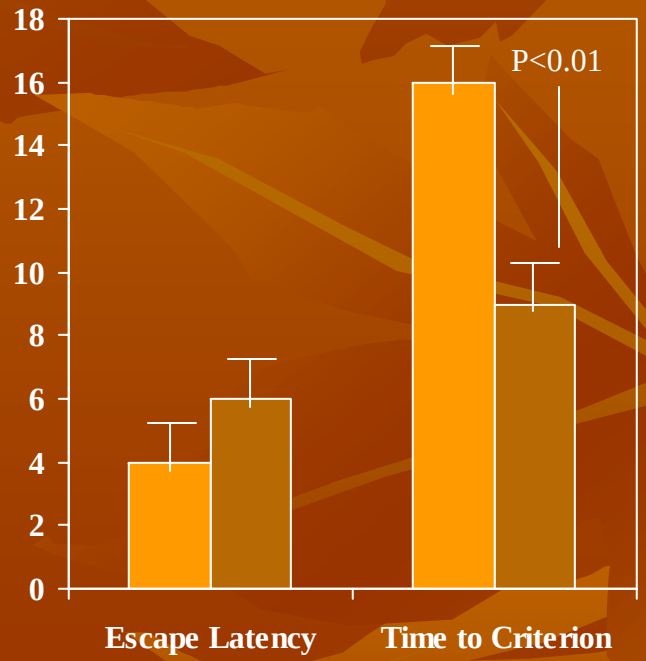
“Memory is a passion
no less powerful or pervasive
than love.”
Elie Wiesel
“All Rivers Run to the Sea”



Effects of CNS Lesion on Acquisition



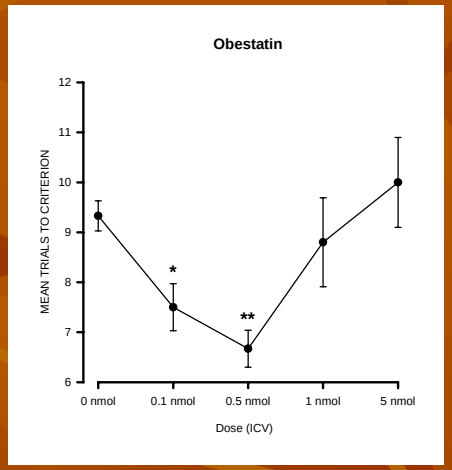
Hippocampal Lesions

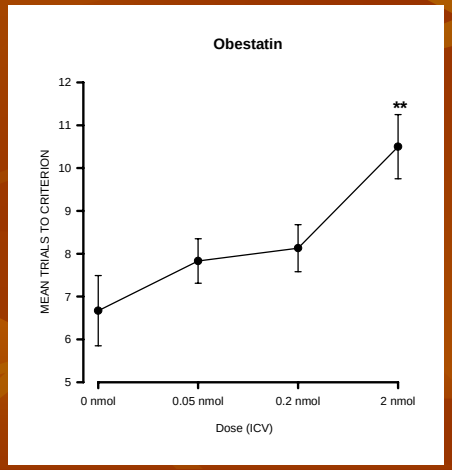


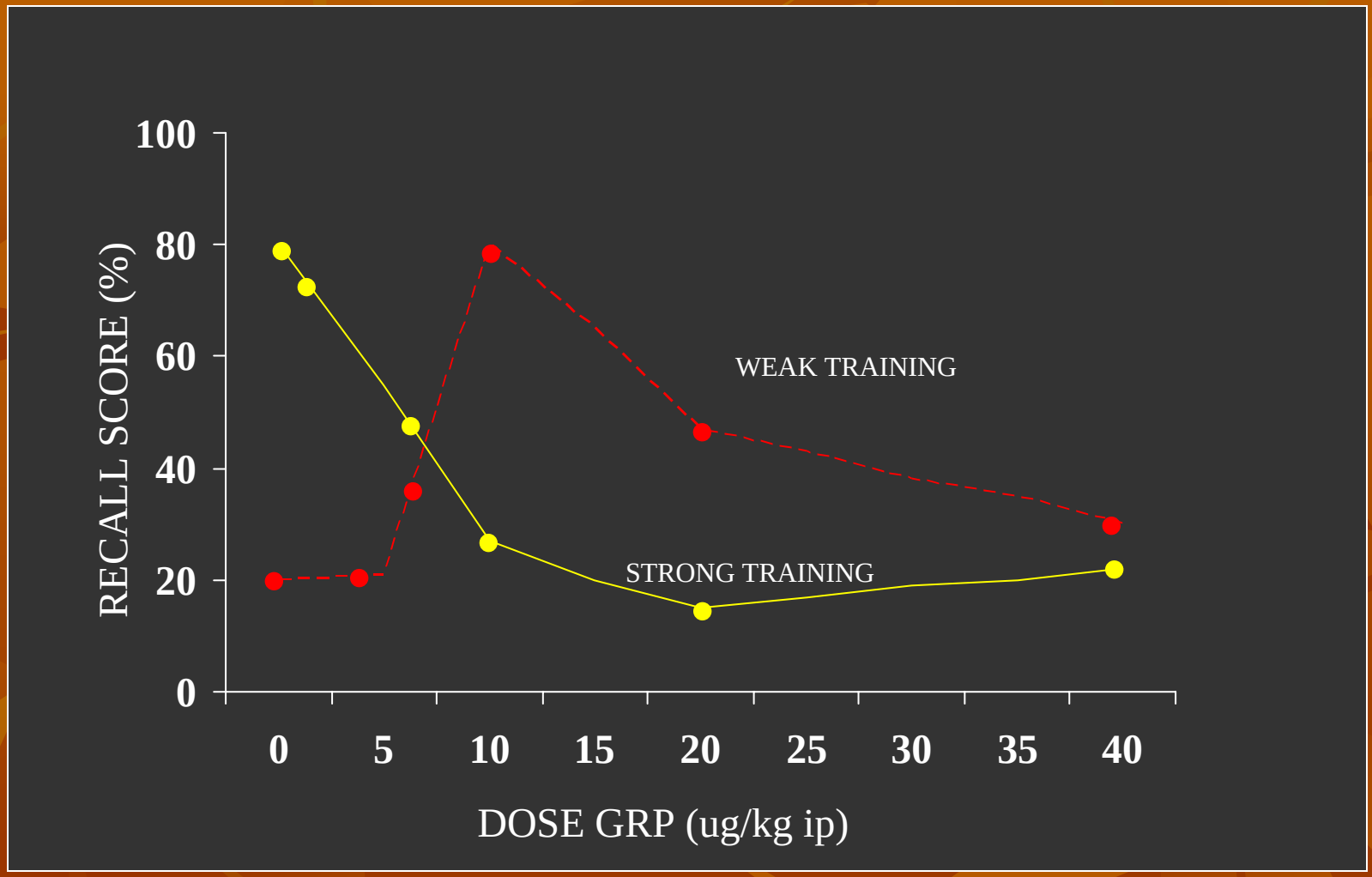
Septal Lesions

THE GOLDEN RULES OF MEMORY ENHANCEMENT

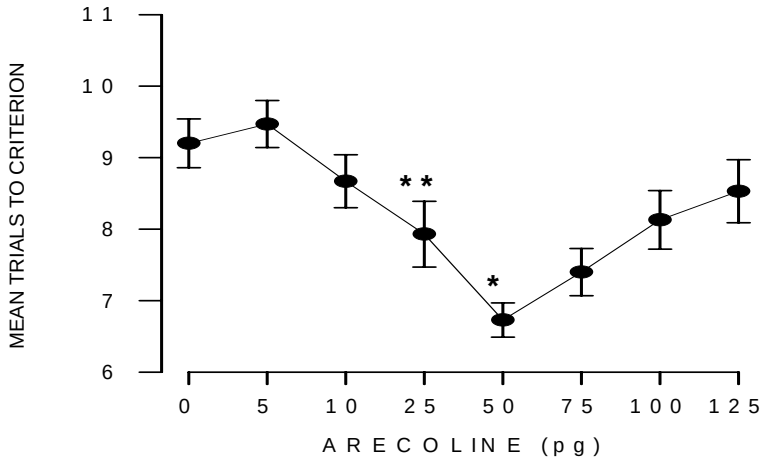
- 1.All memory enhancers impair memory at higher doses.--- Bell shaped or inverted-U dose response
- 2.Memory enhancers impair memory in overtrained animals

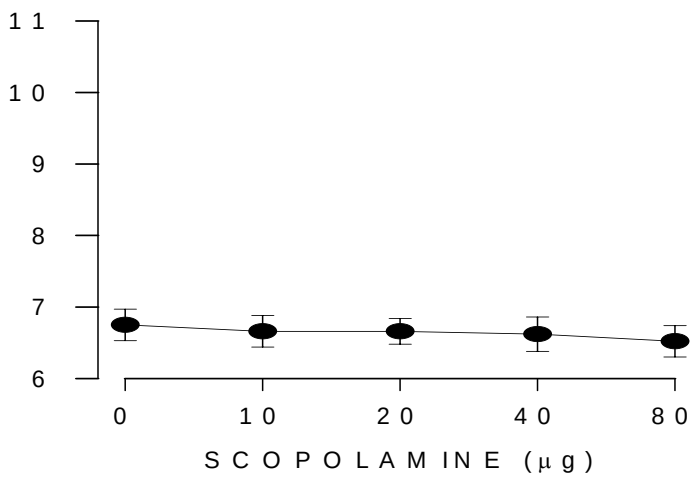


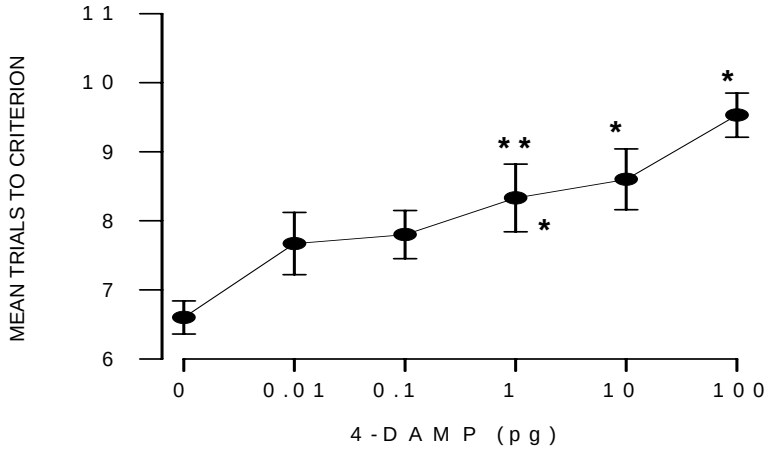


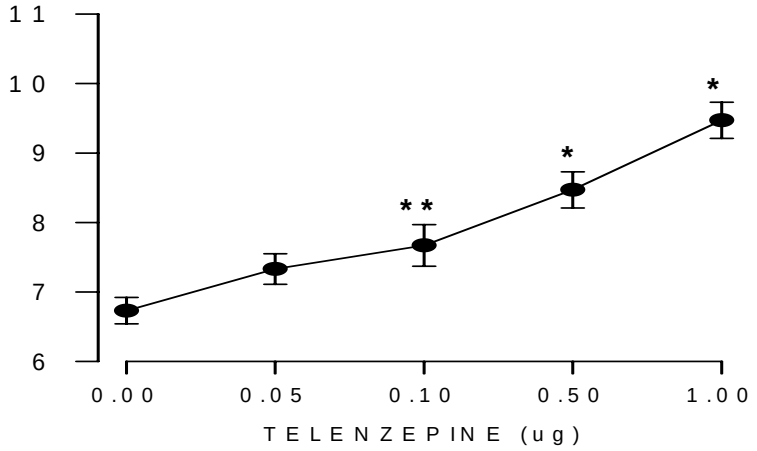

100
80
60
40
20
0
RECALL SCORE (%)
WEAK TRAINING
STRONG TRAINING
0
5
10
15
20
25
30
35
40
DOSE GRP (ug/kg ip)

ACETYLCHOLINE - MUSCARINIC RECEPTOR HIPPOCAMPUS

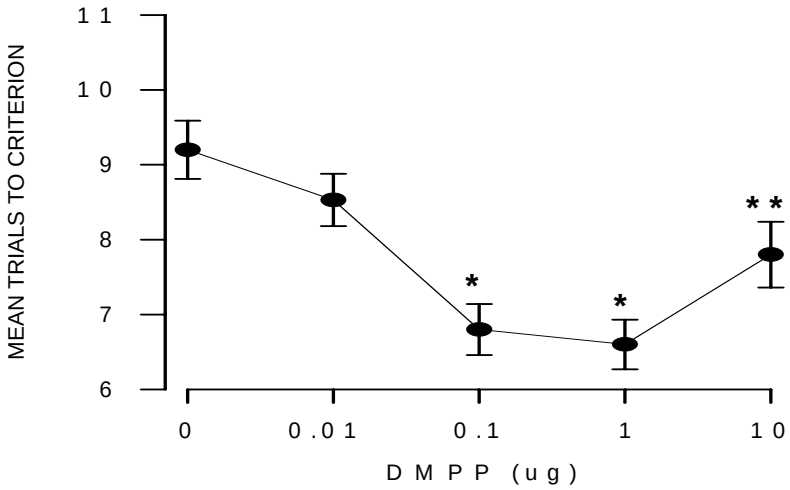


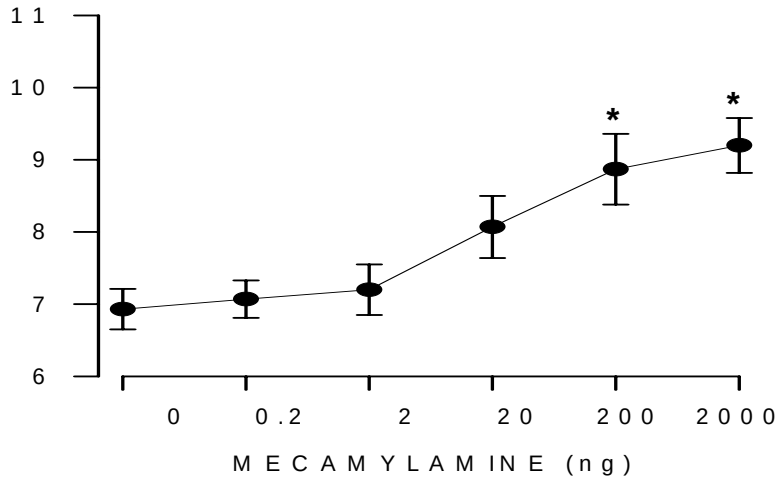






ACETYLCHOLINE HIPPOCAMPUS





Nicotinic Receptor Agonist and Antagonist

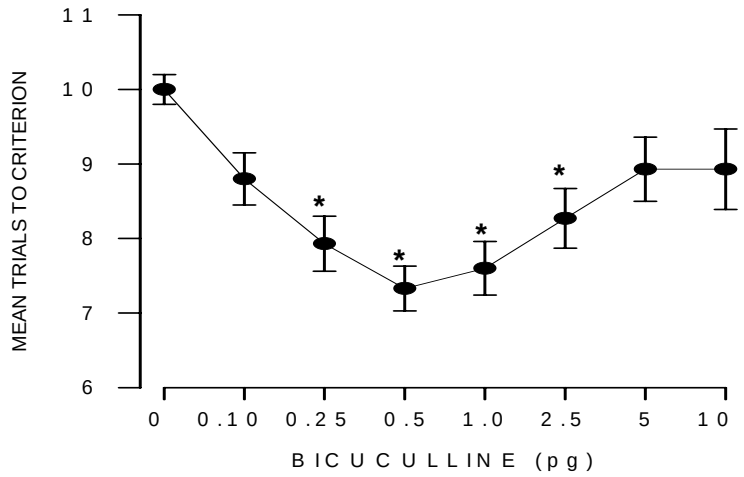
Meta-analysis : Cholinesterase Inhibitors

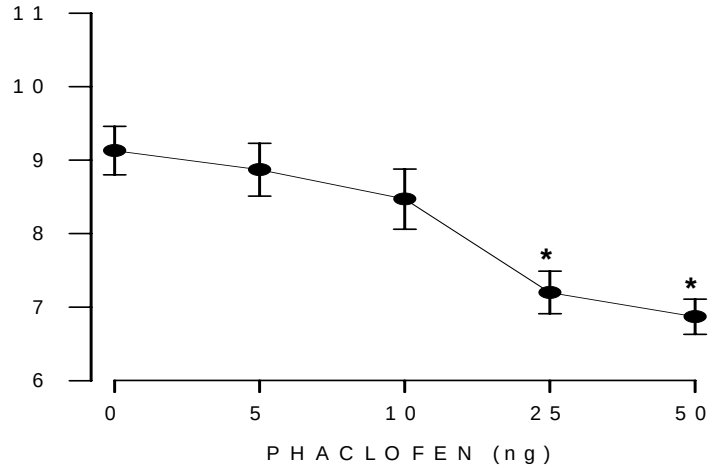
- 9% more global responders to ChEI than placebo; 8% higher adverse events....less with donapezil

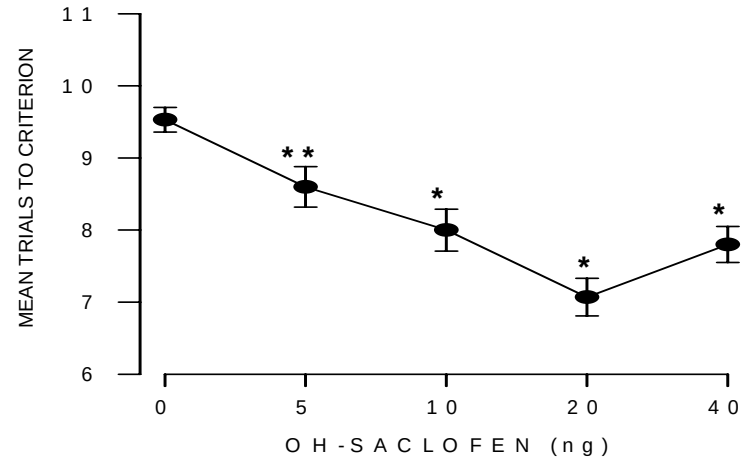
Lanctot et al CMAJ 169:557,2003

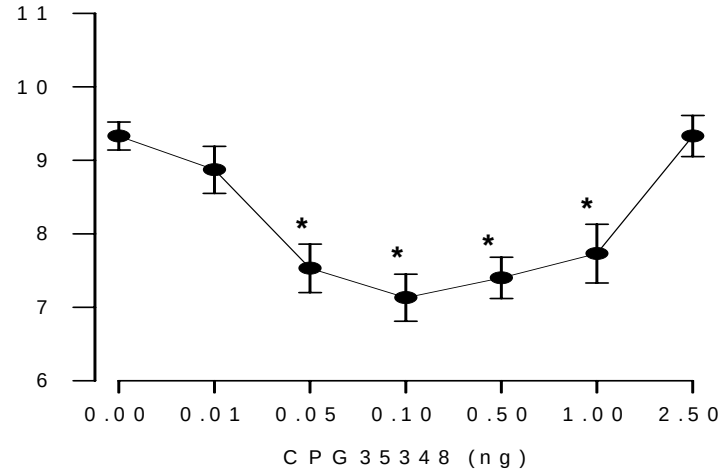
" Flawed methods and small clinical benefits...make recommendations for treatment questionable "

GABA HIPPOCAMPUS



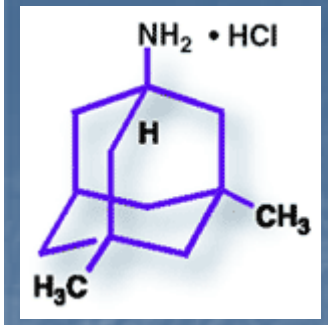






Neuroransmiters demonstrating memory hormesis

- Cholinergic
- GABAergic
- Serotoninergic
- Glutamergic/NMDA
- Histaminergic (H2 & H3)
- Dopaminergic
- Norepinehrinergic



Memantine : Meta-analysis Cochrane Database

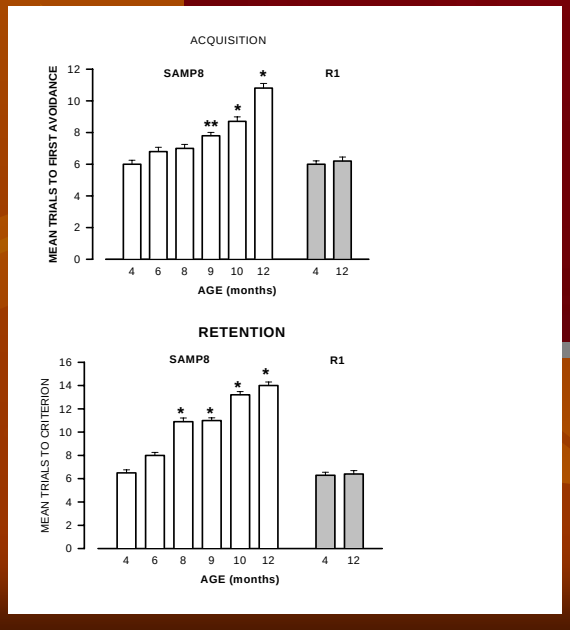
- Improved behavior (2.76/144)
- Improved ADLs (1.27/54)
- Decreased Agitation (8% vs 12%)

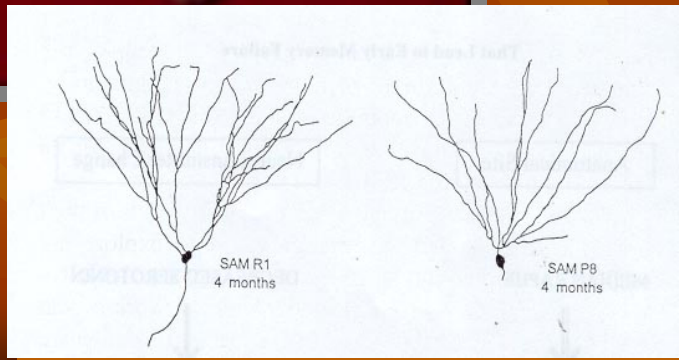
? DUE TO DECREASED NMDA ACTIVITY DECREASING PAIN

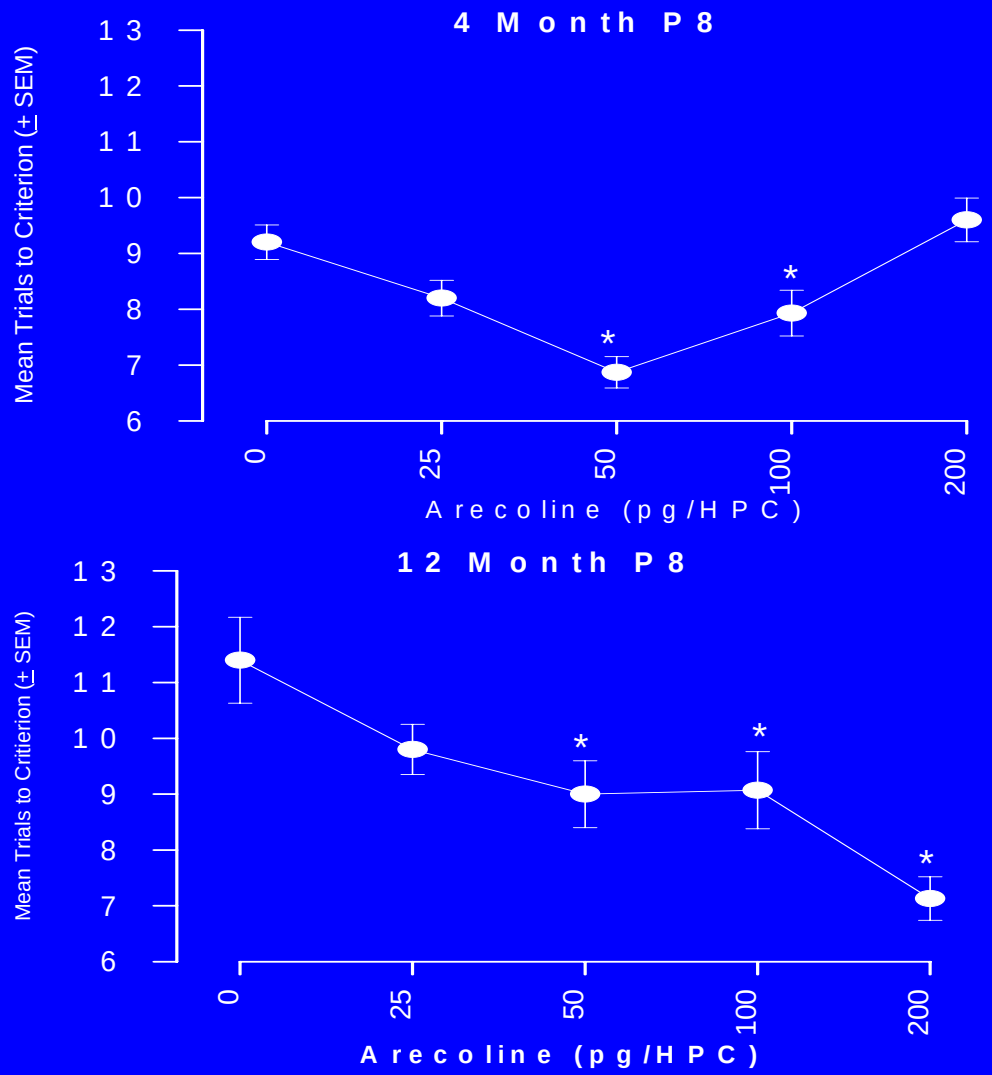
The Third Golden Rule

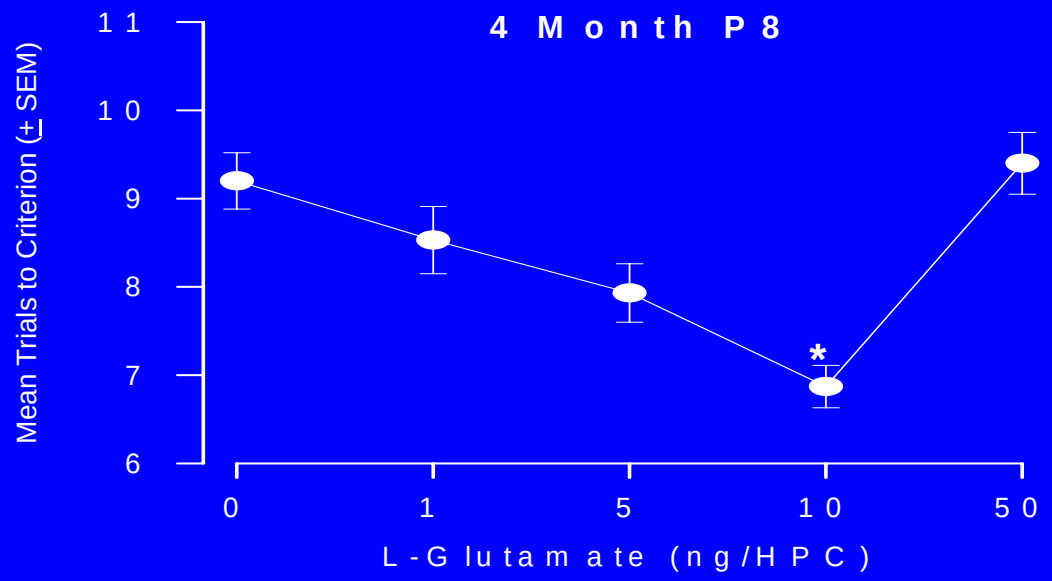
3. Memory impaired animals have altered dose responses curves

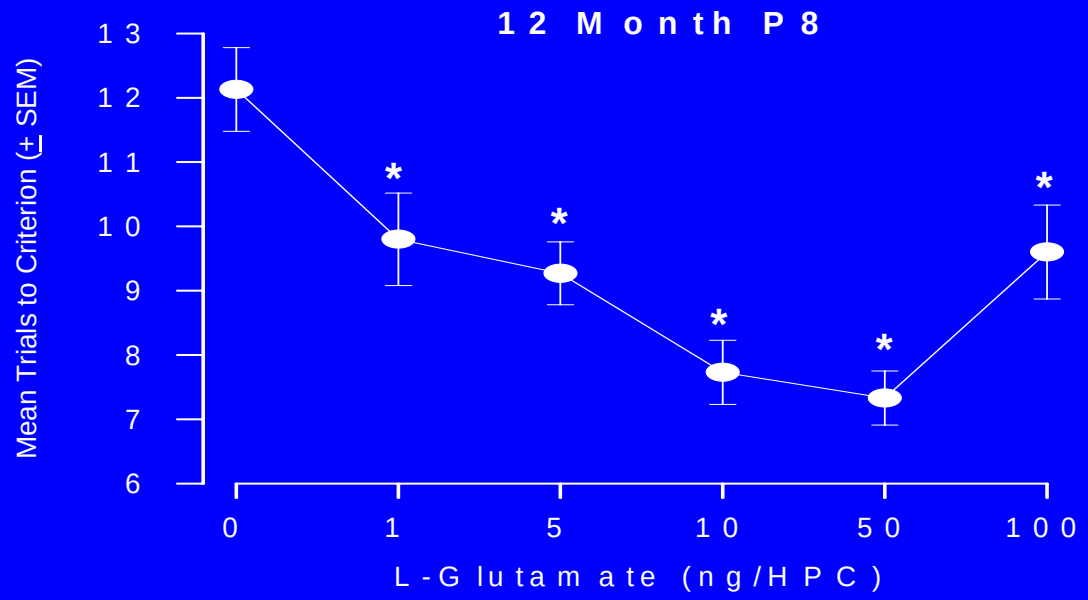
SAMP8 MOUSE


ACQUISITION
SAMP8
R1
MEAN TRIALS TO FIRST AVOIDANCE
AGE (months)
RETENTION
SAMP8
R1
MEAN TRIALS TO CRITERION
AGE (months)

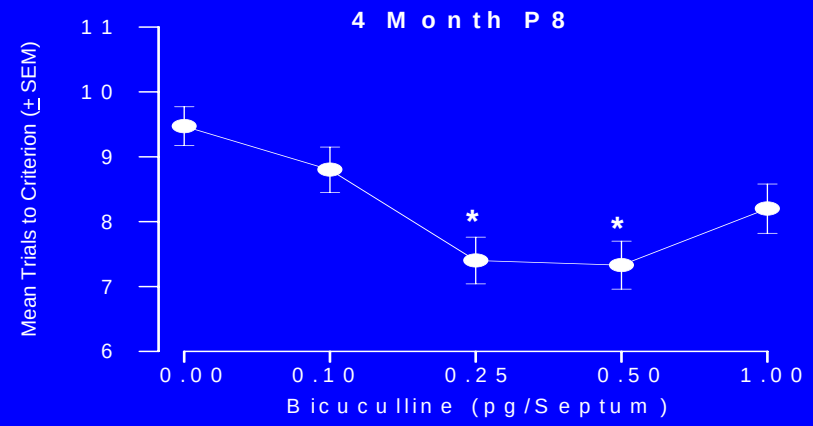

SAM R1
4 months
SAM P8
4 months

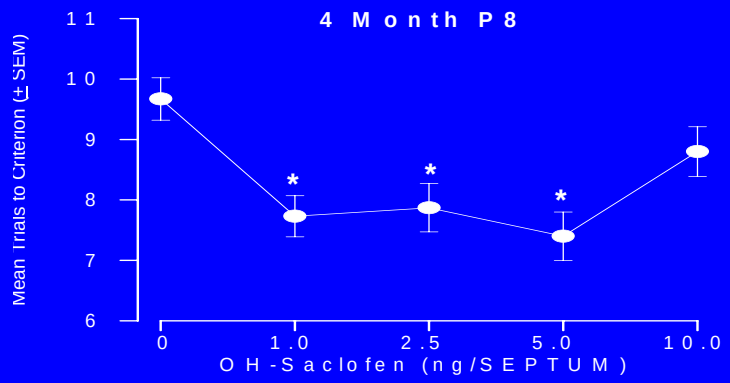

4 Month P8
Mean Trials to Criterion (± SEM)
13
12
11
10
9
8
7
6
0
25
50
100
200
Arecoline (pg/HPC)
*
*
12 Month P8
Mean Trials to Critierion (± SEM)
13
12
11
10
9
8
7
6
0
25
50
100
200
Arecoline (pg/HPC)
*
*
*

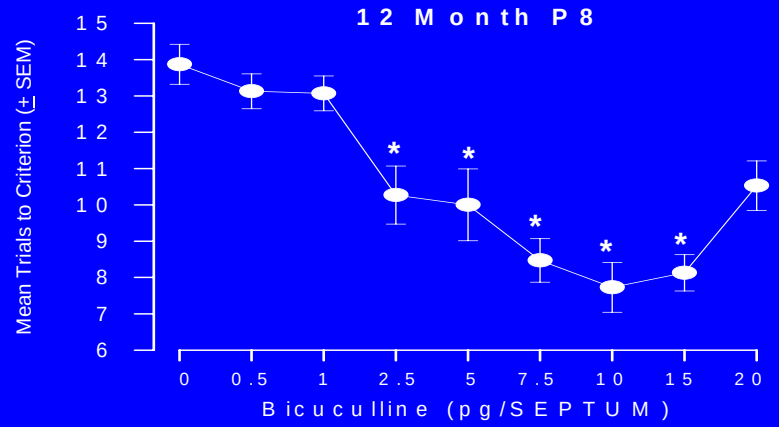

4 Month P8
Mean Trials to Criterion (± SEM)
11
10
9
8
7
6
*
0
1
5
10
50
L-Glutamate (ng/HPC)

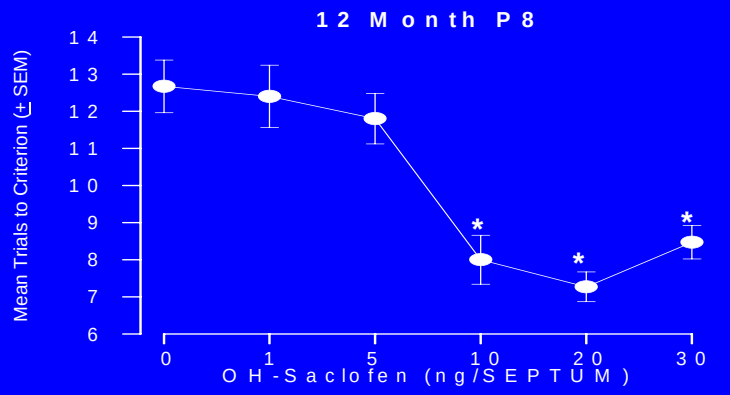

12 Month P8
Mean Trials to Criterion (± SEM)
13
12
11
10
9
8
7
6
*
*
*
*
*
0
1
5
10
50
100
L-Glutamate (ng/HPC)

GABA ANTAGONISTS (GABA-A & GABA-B)

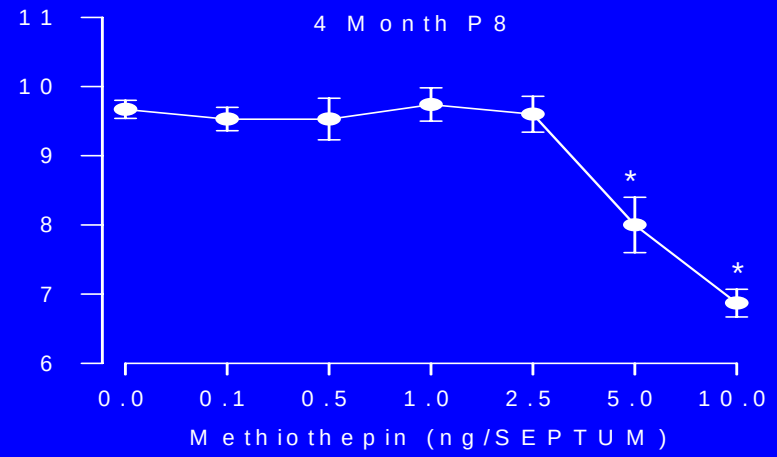


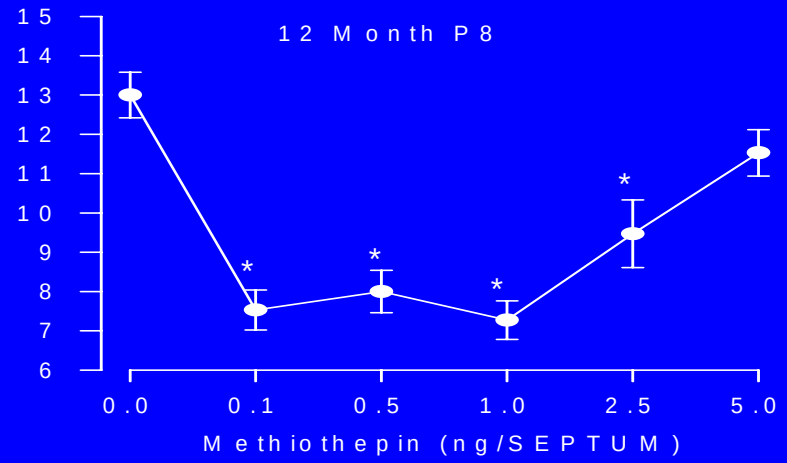


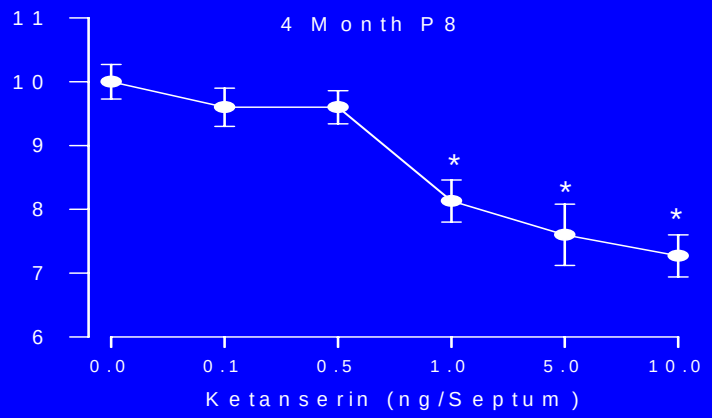


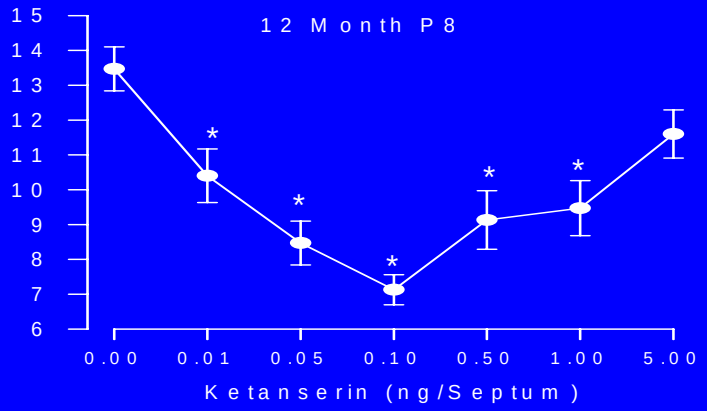


SEROTONIN ANTAGONISTS (HT-1 & HT-2)

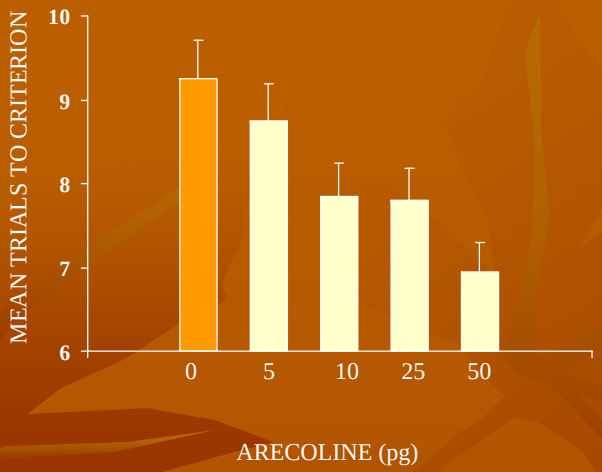


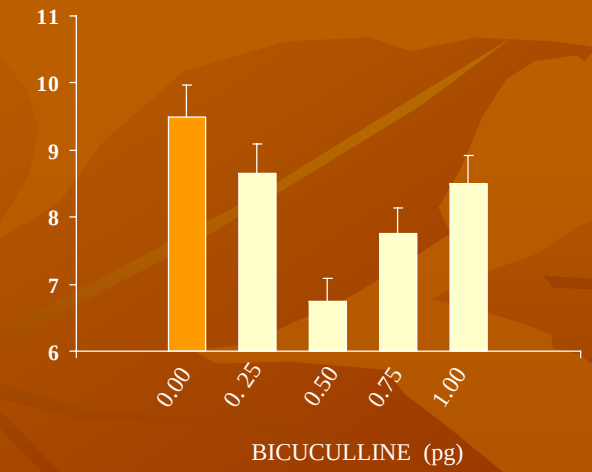


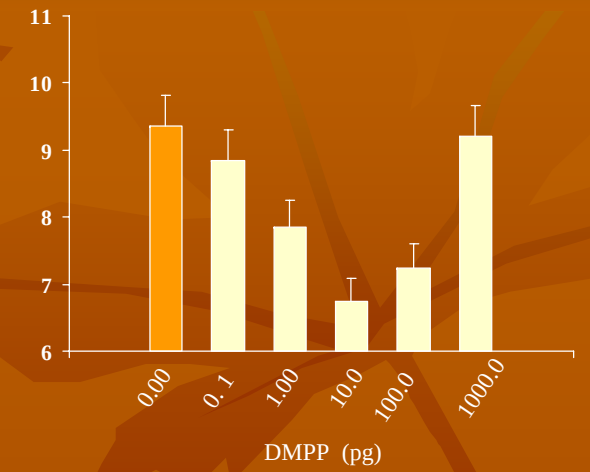


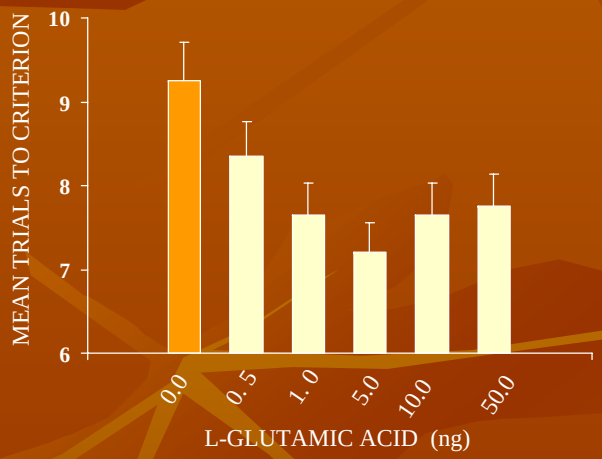


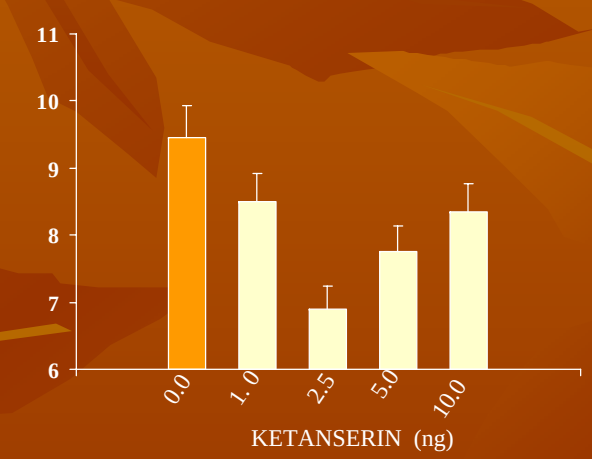
MAMILLARY COMPLEX

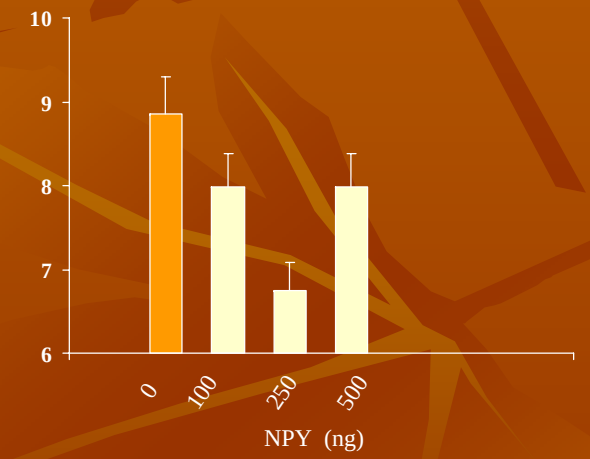


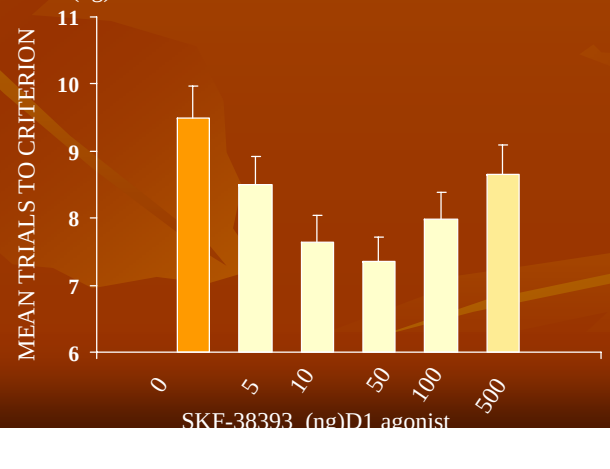


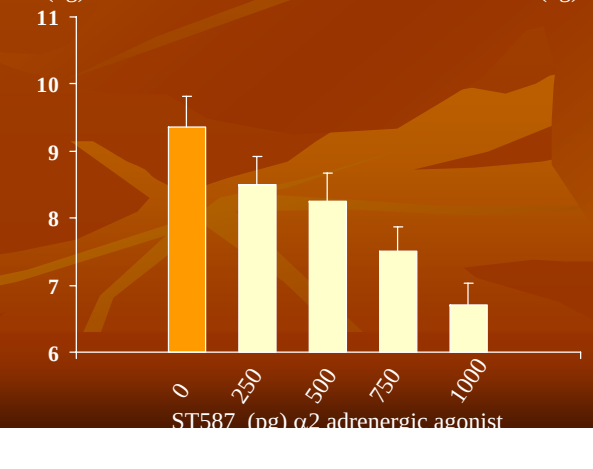








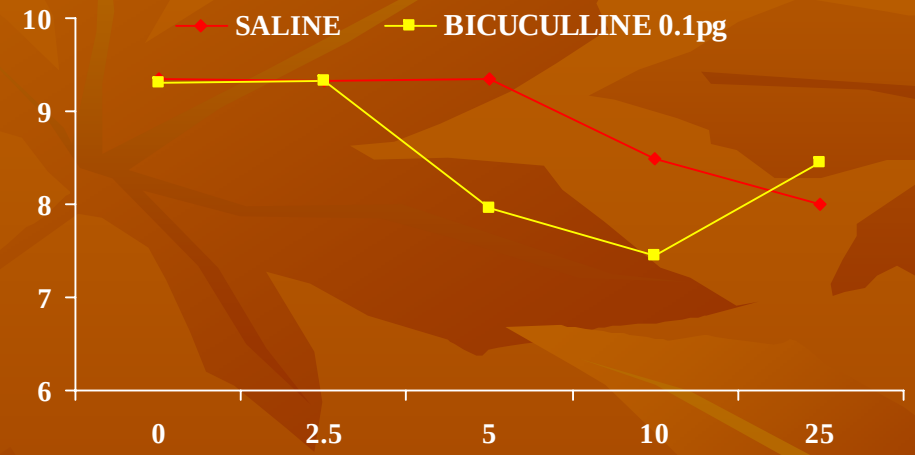


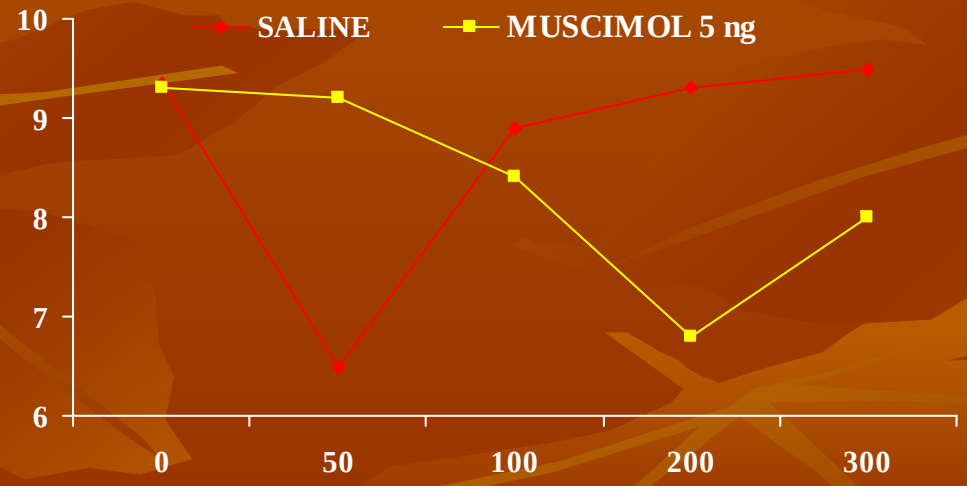


Hormesis is present in multiple brain sites

- Hippocampus
- Septum
- Mammillary bodies
- Amygdala
- Cingulate cortex

CO-ADMINISTERED
Arecoline into hippocampus;
GABA antagonist/agonist into septum



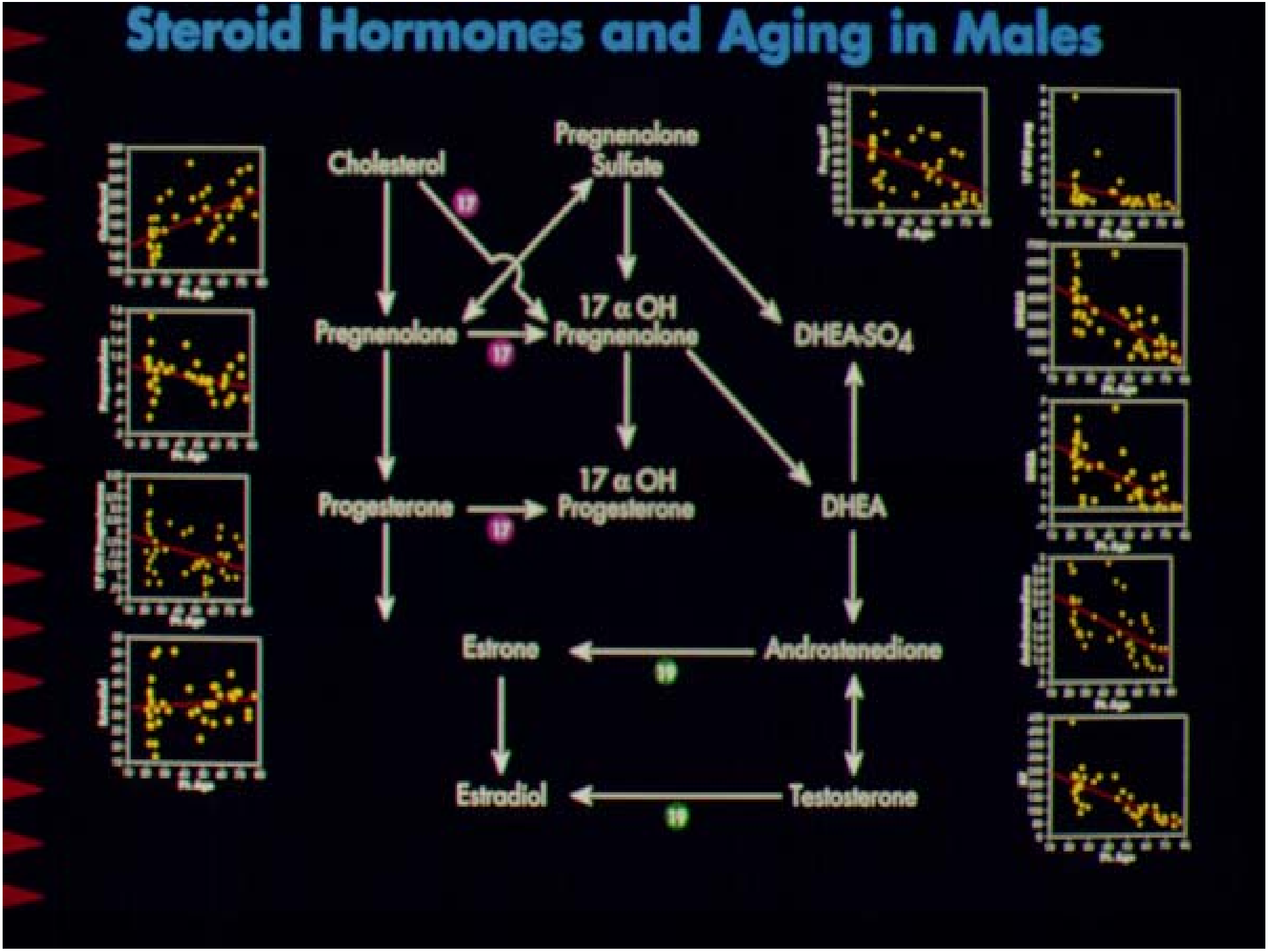


Arecoline (pg)

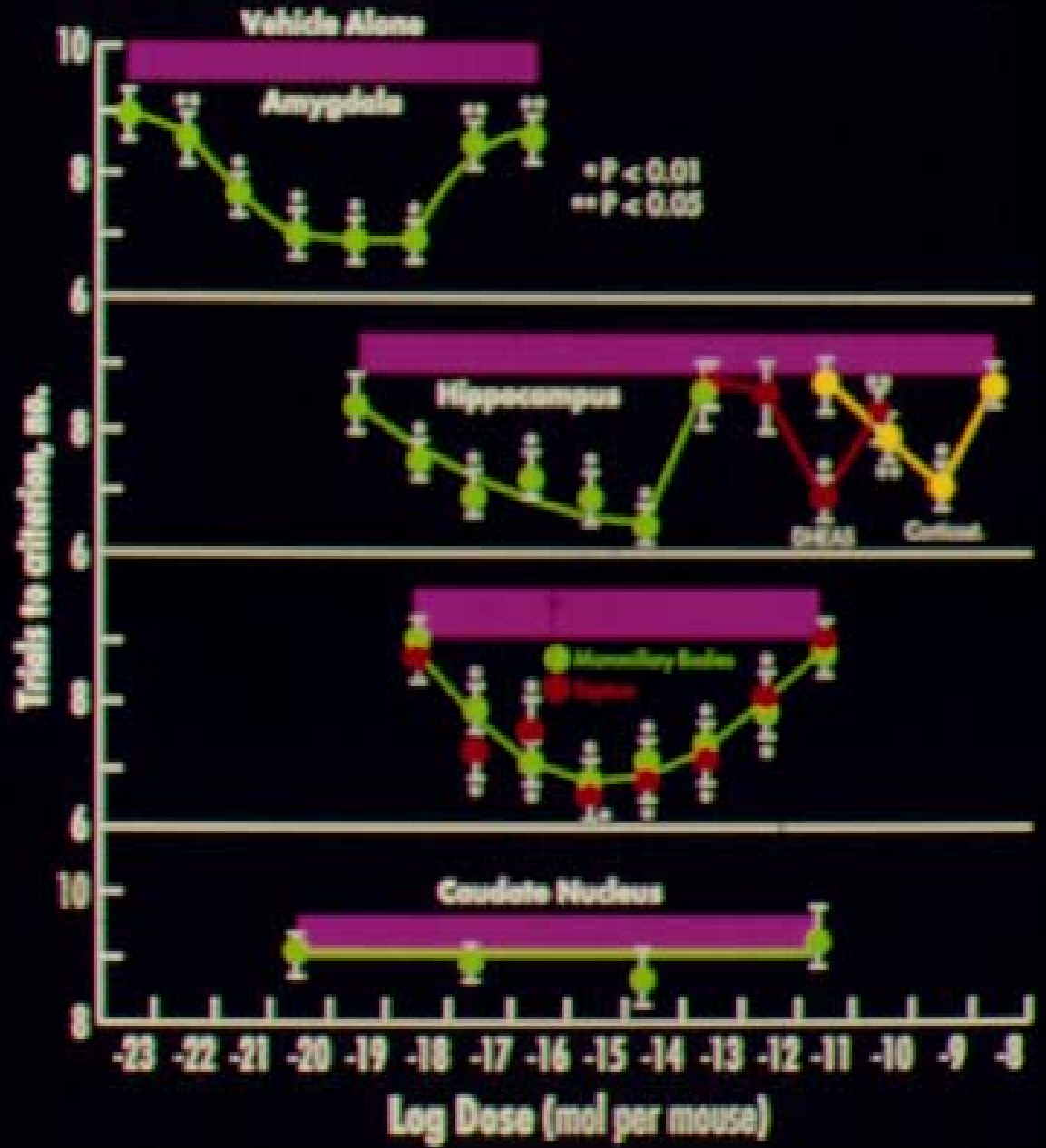
The Fourth Golden Rule

Hormones that modulate memory
follow the laws of hormesis

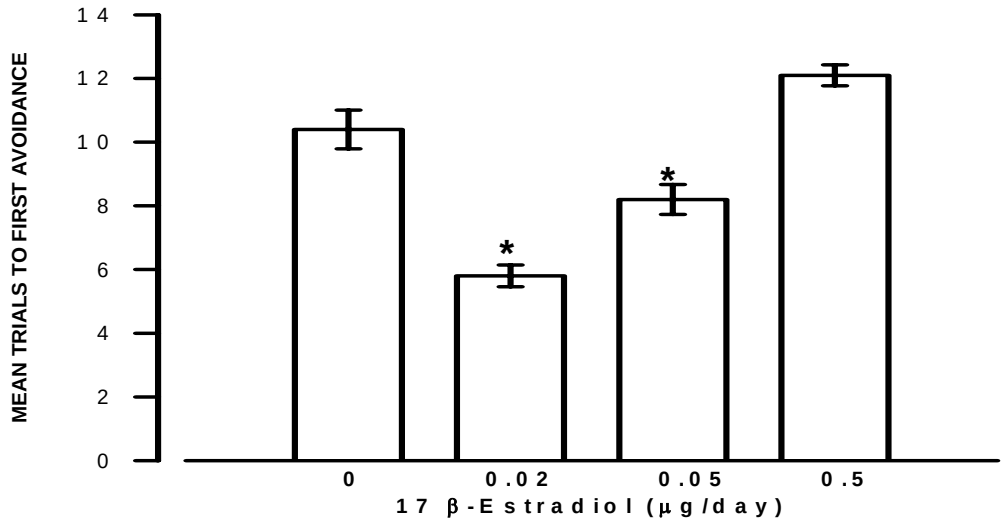
Steroid Hormones and Aging in Males

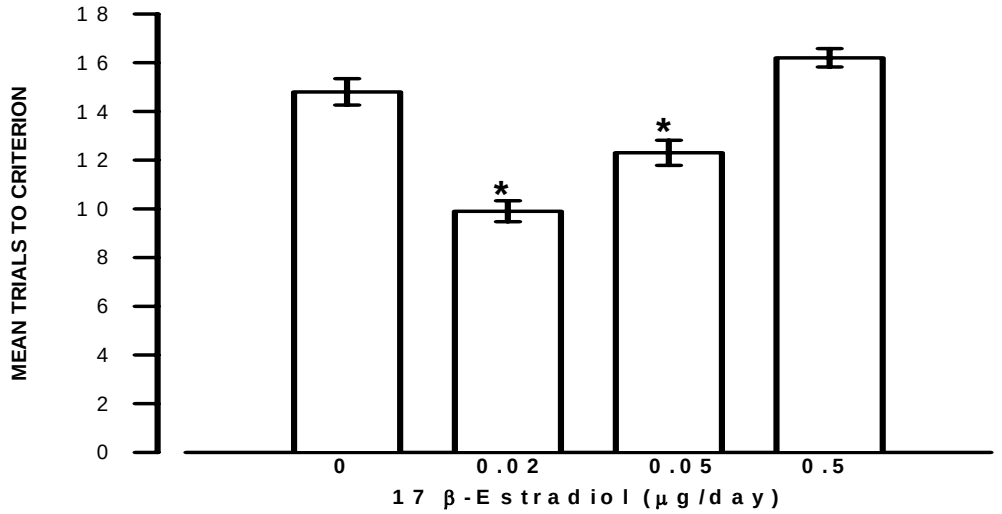


Pregnenolone and Memory

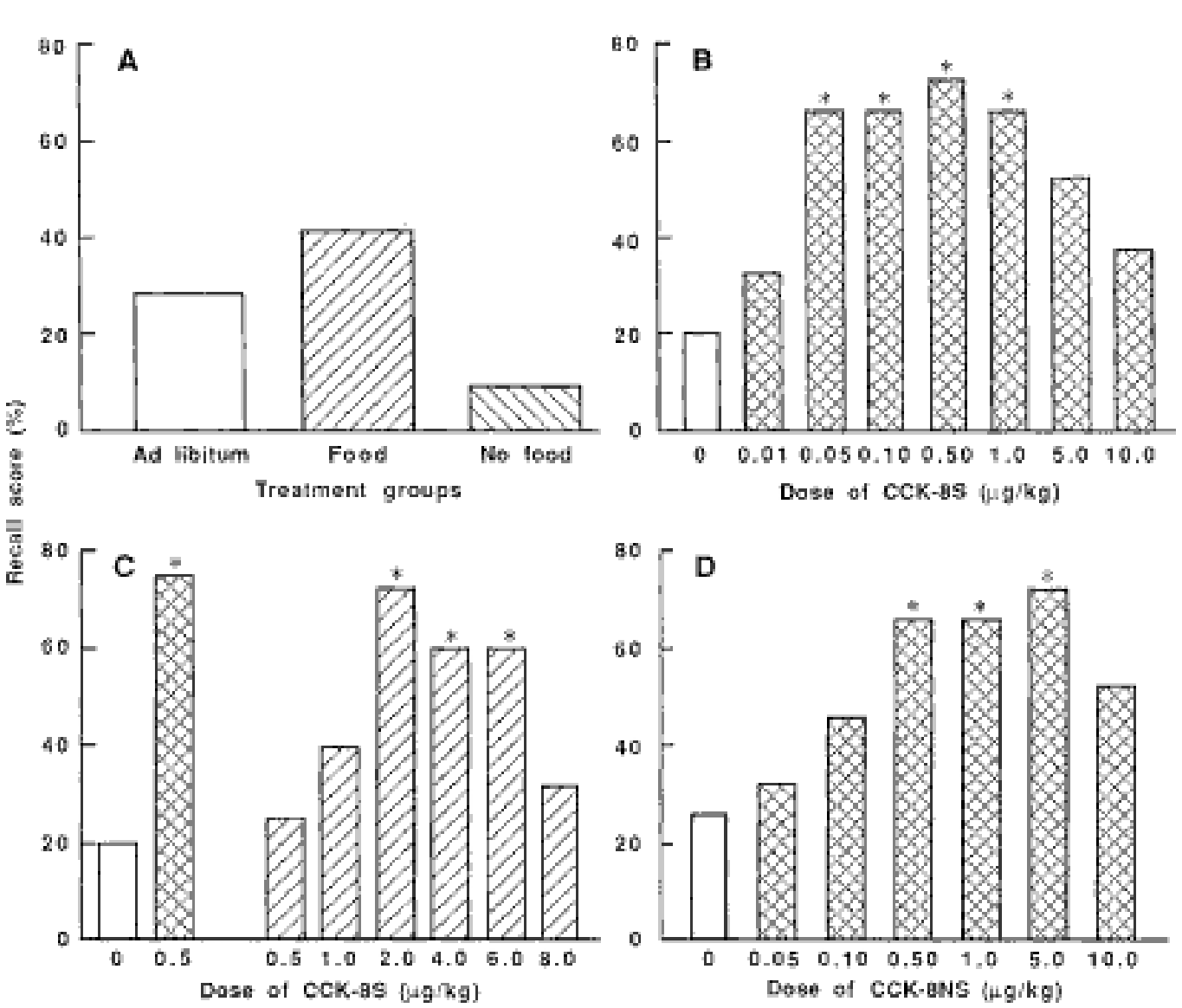


EFFECT OF ESTRADIOL ON ACQUISITION
IN 12 MONTH SAMP8 FEMALE MICE





Food increases memory by releasing CCK

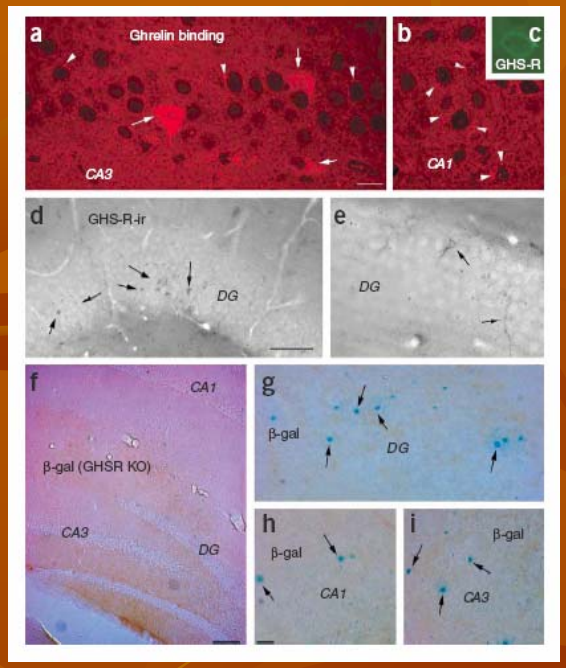


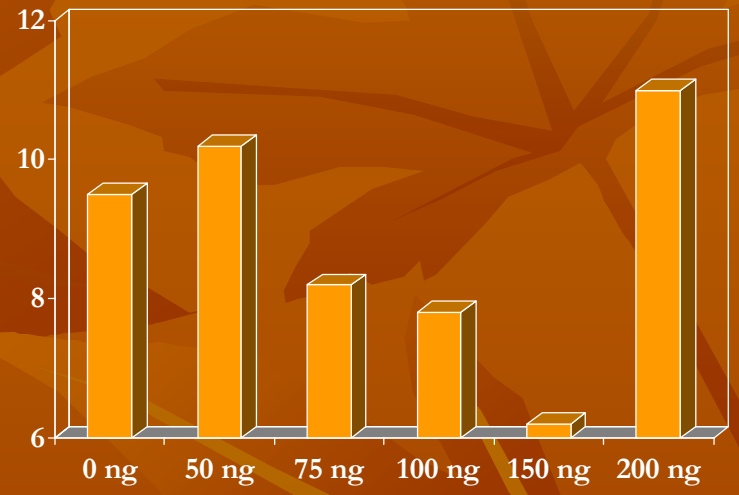
The Gut-Brain Axis

- Acquisition and retention of memories are enhanced by feeding immediately after learning and decreased by feeding prior to training
- Cholecystokinin enhances acquisition and memory with a bell-shaped dose response curve by activating the ascending fibers of the vagus.The pathway is Duodenum-vagus-NTS-amygdala-hippocampus
- Blocking the effect of cholecystokinin blocks the effect of feeding on memory

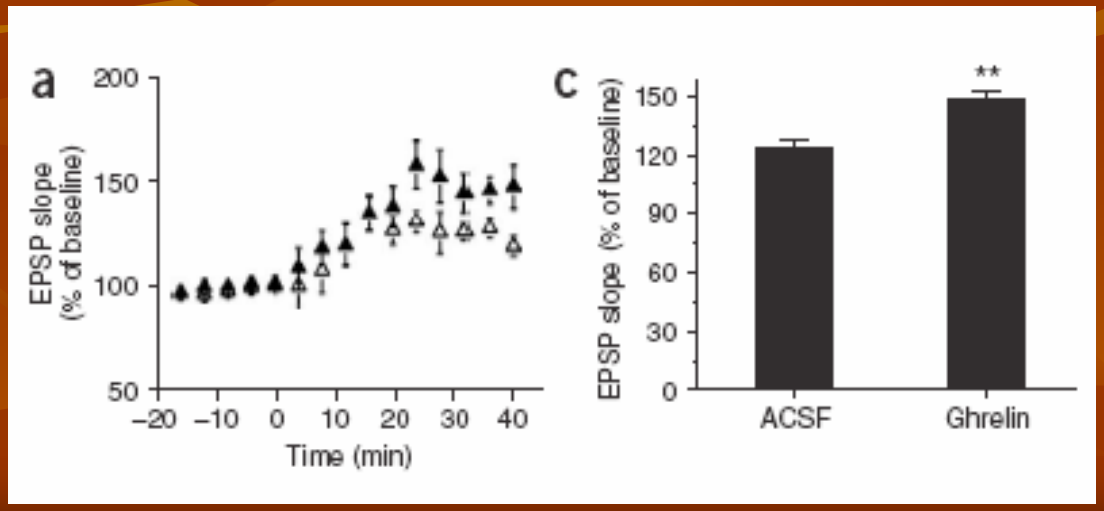
Science 15:832,1987
Neurobiol Learn Mem 64:139
Brain Res 10:585,1992

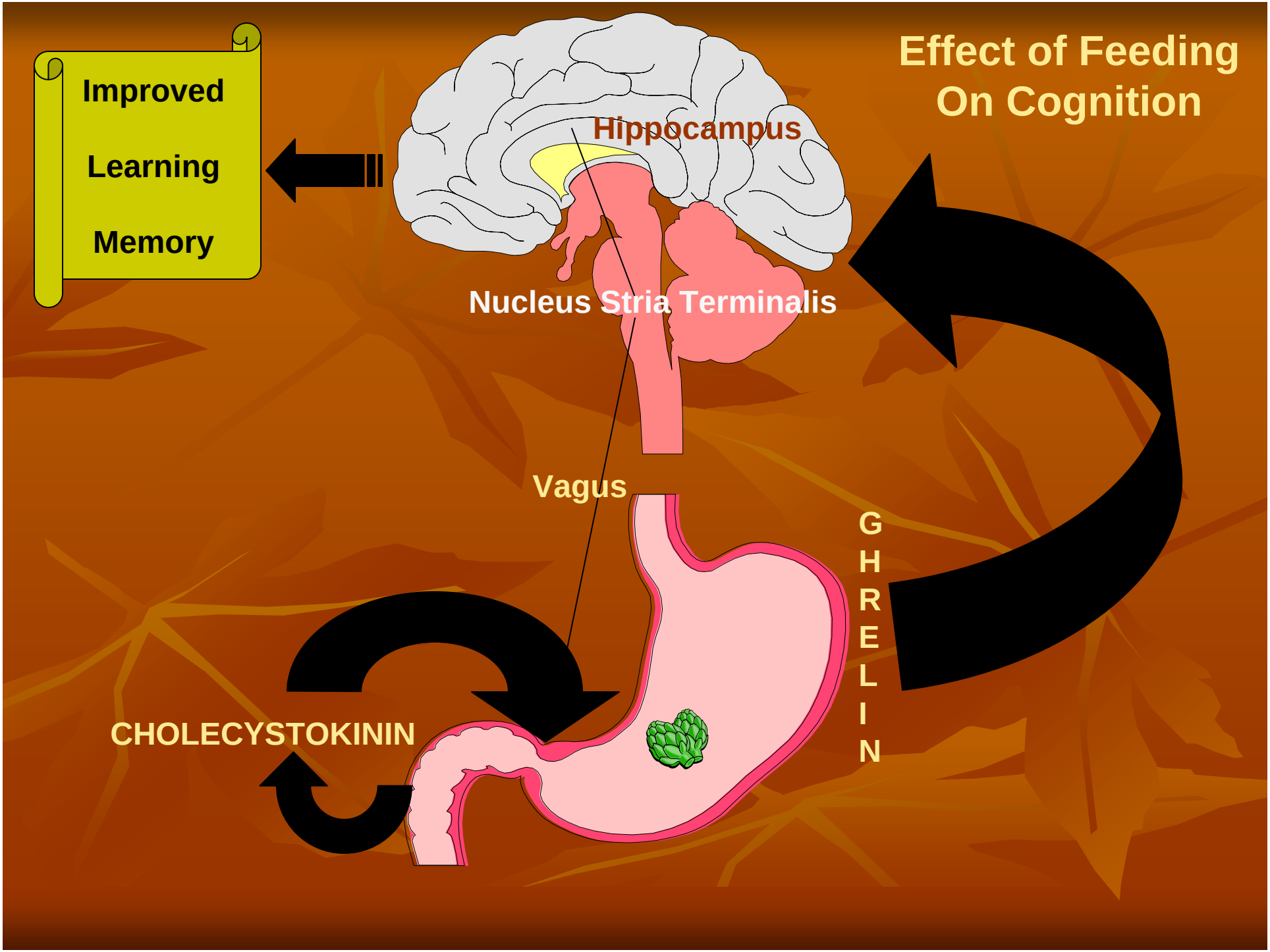
Ghrelin Enhances Memory



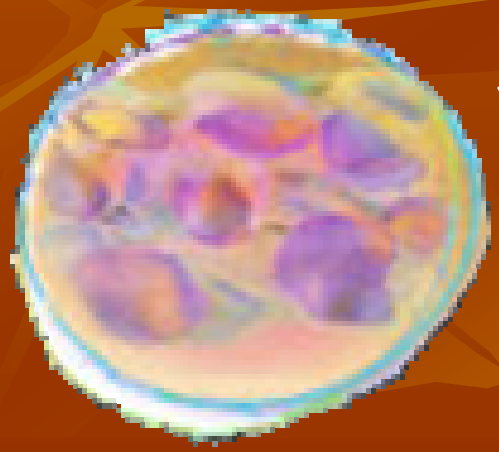


Nature Neuroscience 2006



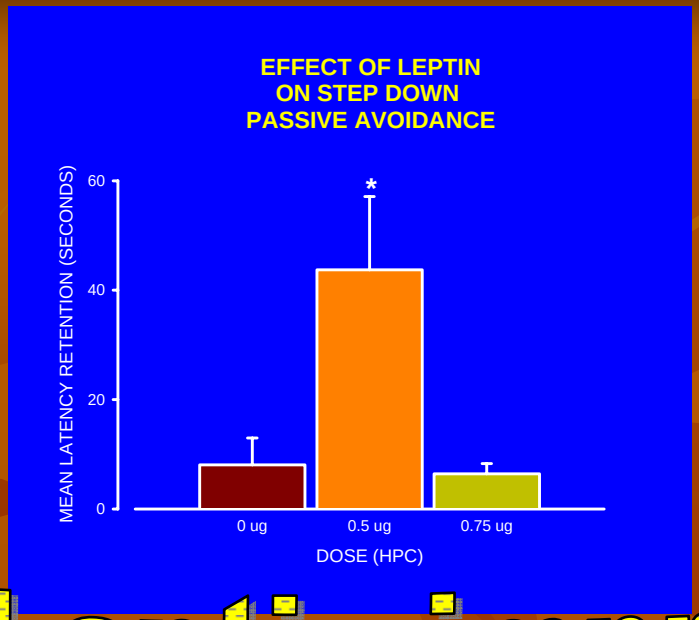

Effect of Feeding
On Cognition
Improved
Learning
Memory
Hippocampus
Nucleus Stria Terminalis
Vagus
GHRELIN
CHOLECYSTOKININ

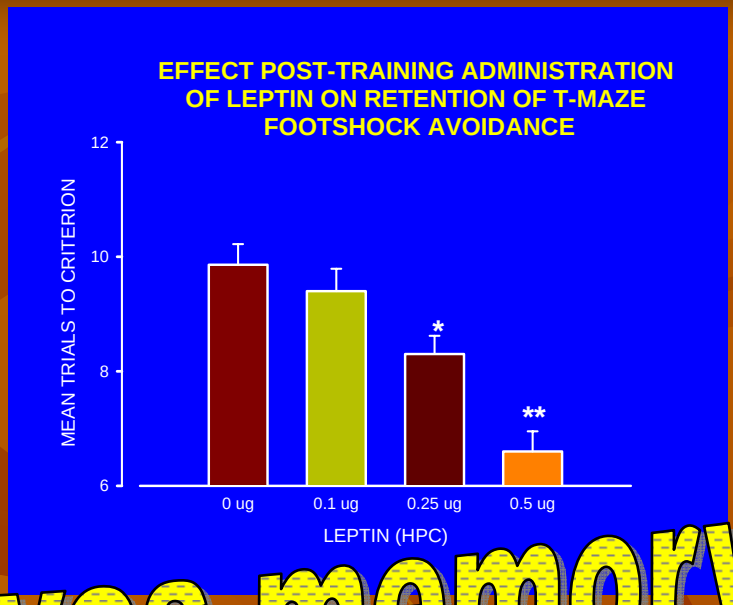
The Fat-Brain Axis

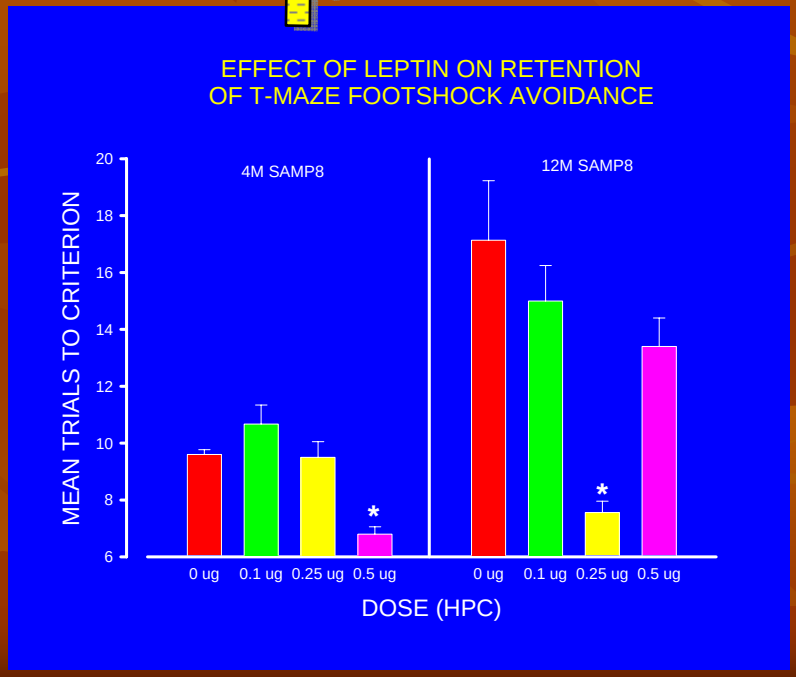


LEPTIN

Leptin improves memory

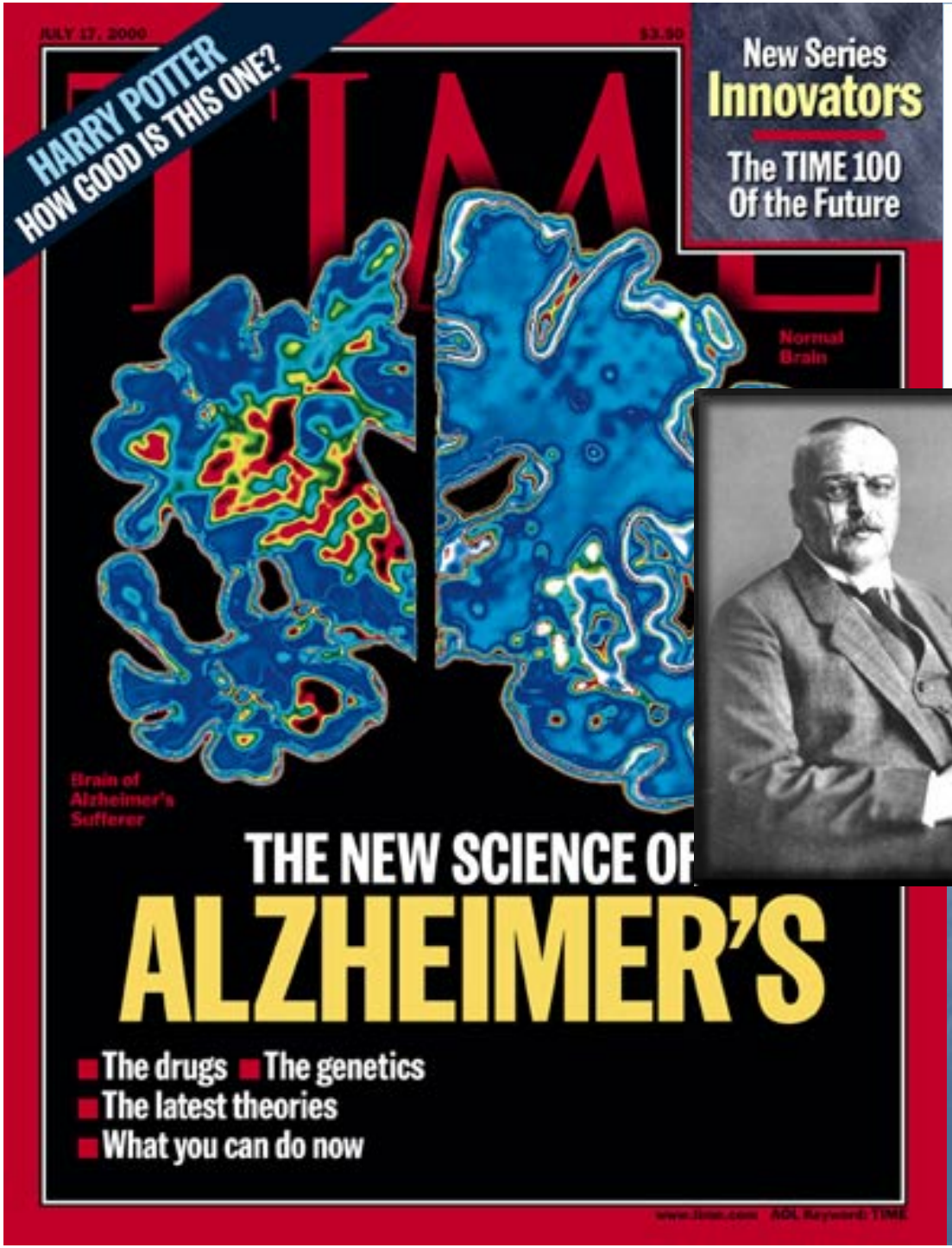


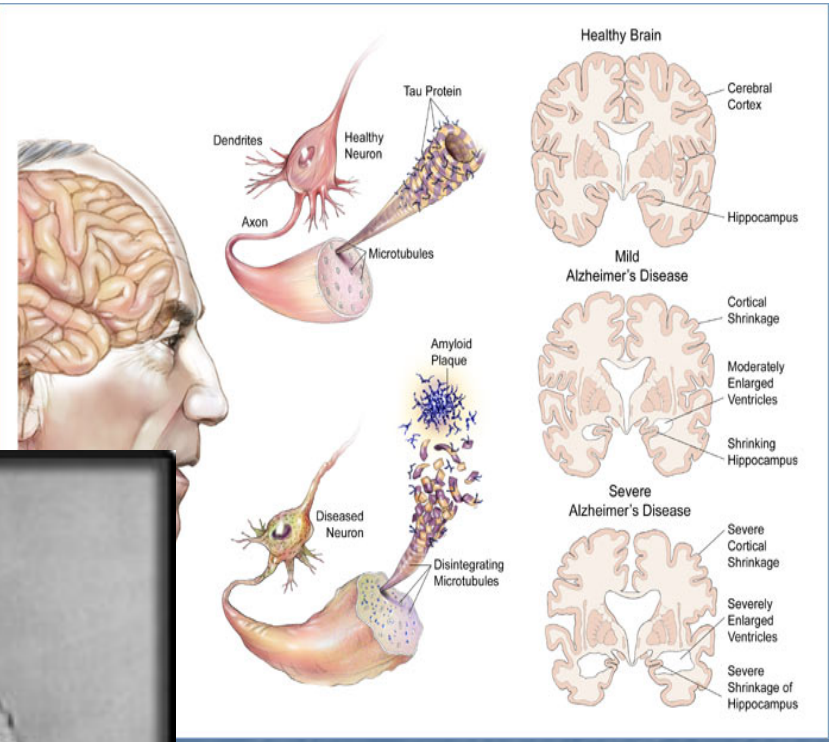


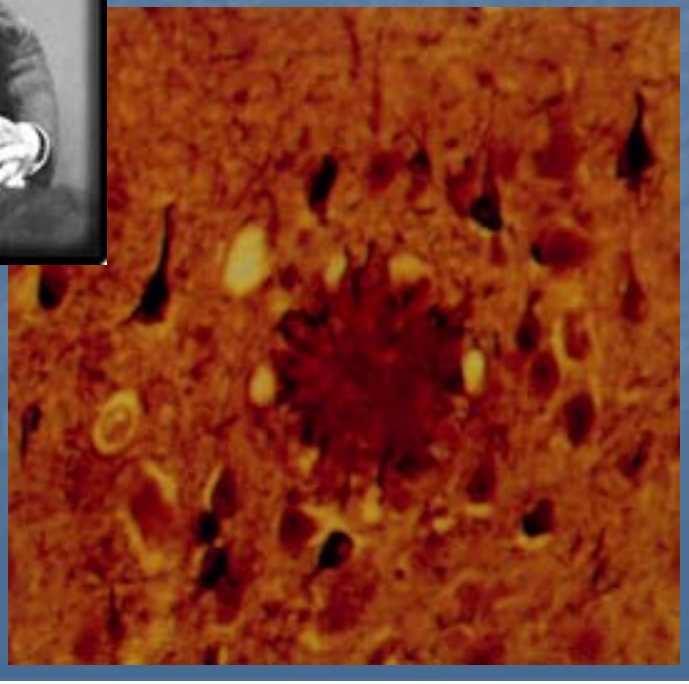


The Fifth Golden Rule

Peptides given peripherally or centrally (eg NPY,NPK) follow the laws of hormesis

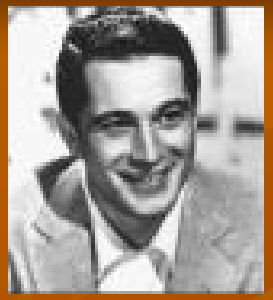

JULY 17, 2000
$3.50
HARRY POTTER
HOW GOOD IS THIS ONE?
New Series
Innovators
The TIME 100
Of the Future
Normal Brain
Brain of Alzheimer's Sufferer
THE NEW SCIENCE OF
ALZHEIMER'S
The drugs
The genetics
The latest theories
What you can do now


Tau Protein
Dendrites
Healthy Neuron
Axon
Microtubules
Amyloid Plaque
Diseased Neuron
Disintegrating Microtubules
Healthy Brain
Cerebral Cortex
Hippocampus
Mild Alzheimer's Disease
Cortical Shrinkage
Moderately Enlarged Ventricles
Shrinking Hippocampus
Severe Alzheimer's Disease
Severe Cortical Shrinkage
Severely Enlarged Ventricles
Severe Shrinkage of Hippocampus



Famous People with Alzheimer's

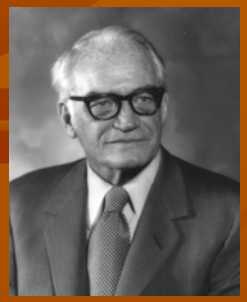
Charles Bronson



Perry Como

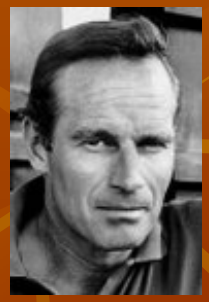
Thomas Dorsey

Rita Hayworth



Barry Goldwater

Norman Rockwell



Charlton Heston

Sugar Ray Robinson

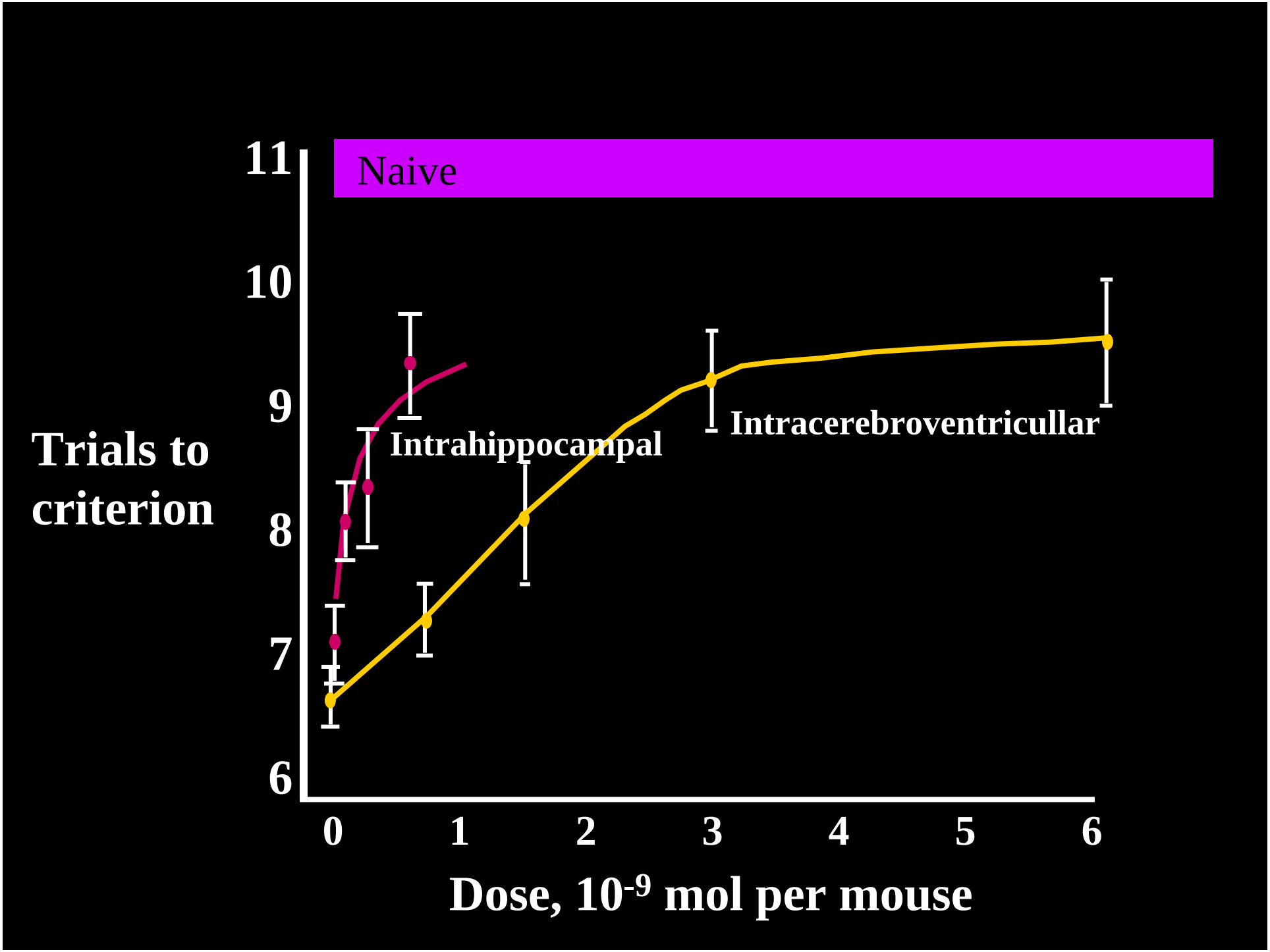
Iris Murdoch

Ronald Reagan

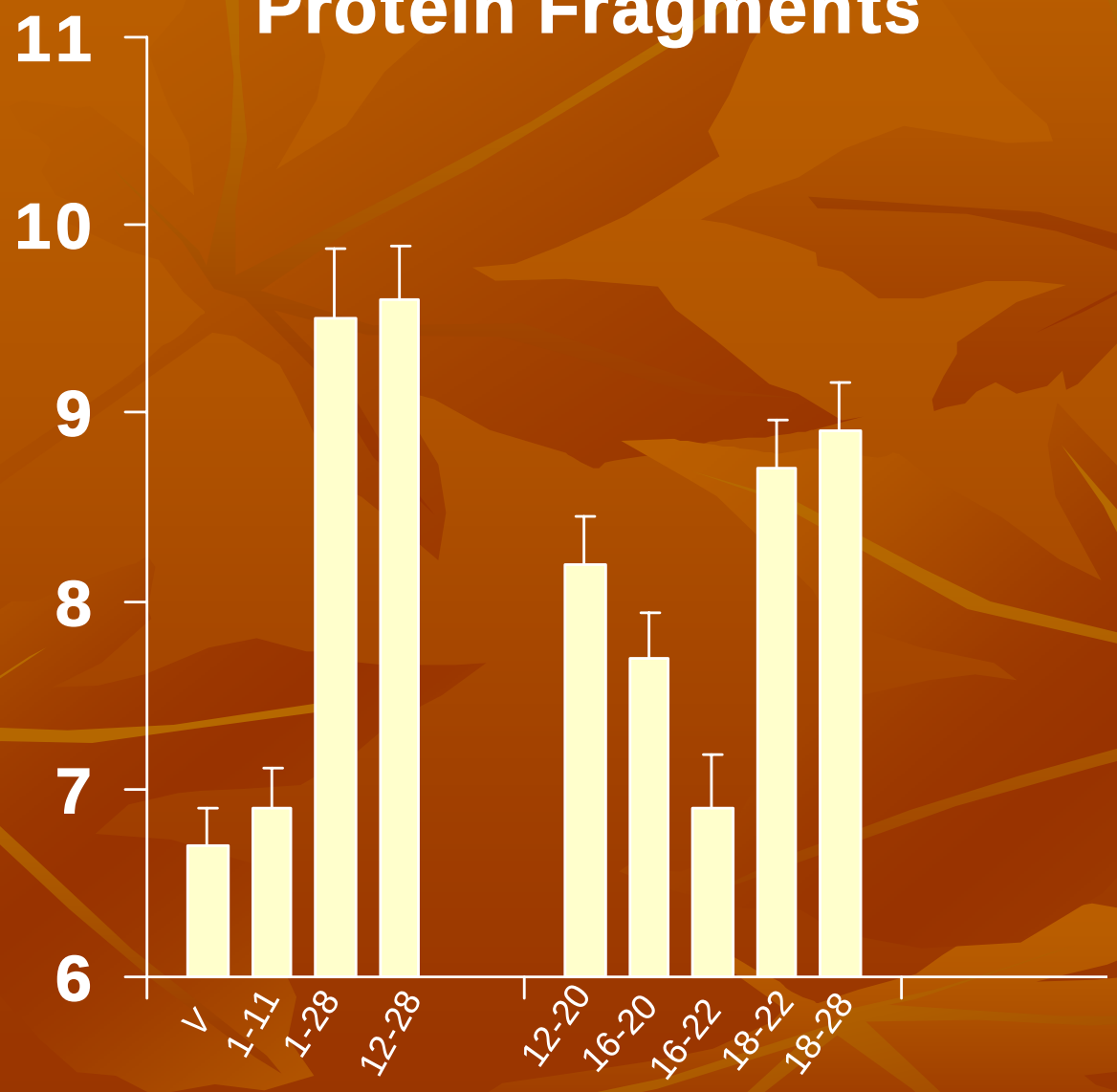
Alfred Van Vogt

Amyloid Beta Protein:

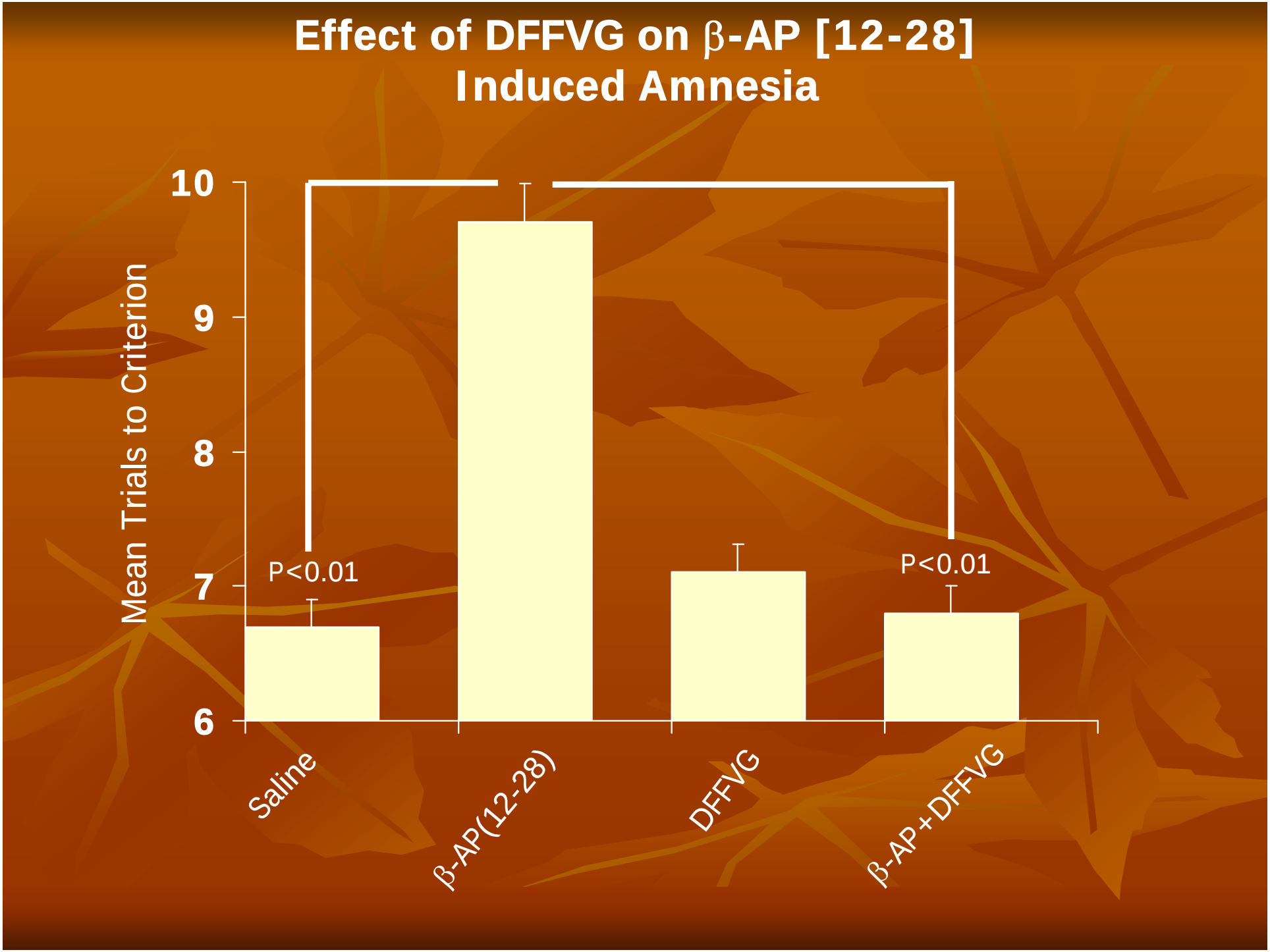
Learning and Memory


Naive
11
10
9
8
7
6
Trials to criterion
Intrahippocampal
Intracerebroventricullar
0
1
2
3
4
5
6
Dose, 10-9 mol per mouse

Selective Amnestic Effects by β-Amyloid Protein Fragments

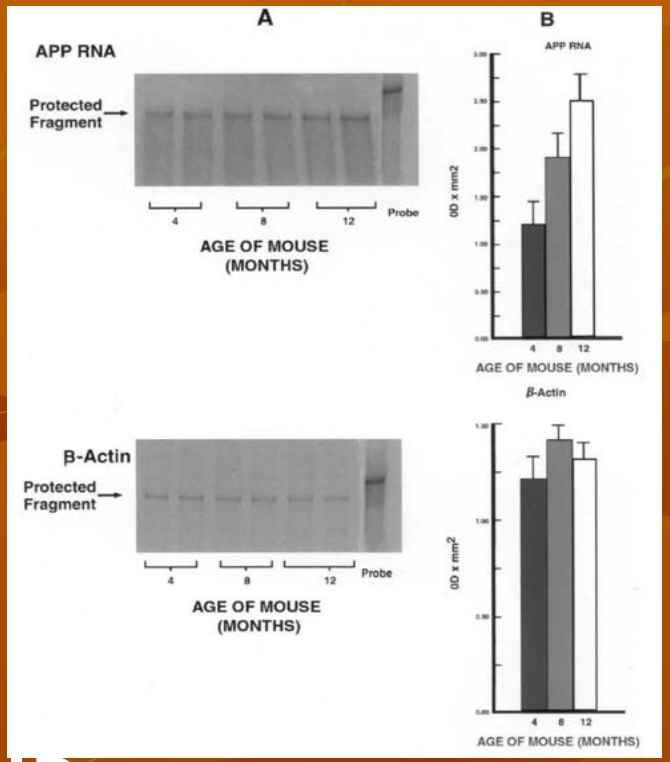


Effect of DFFVG on β-AP [12-28] Induced Amnesia

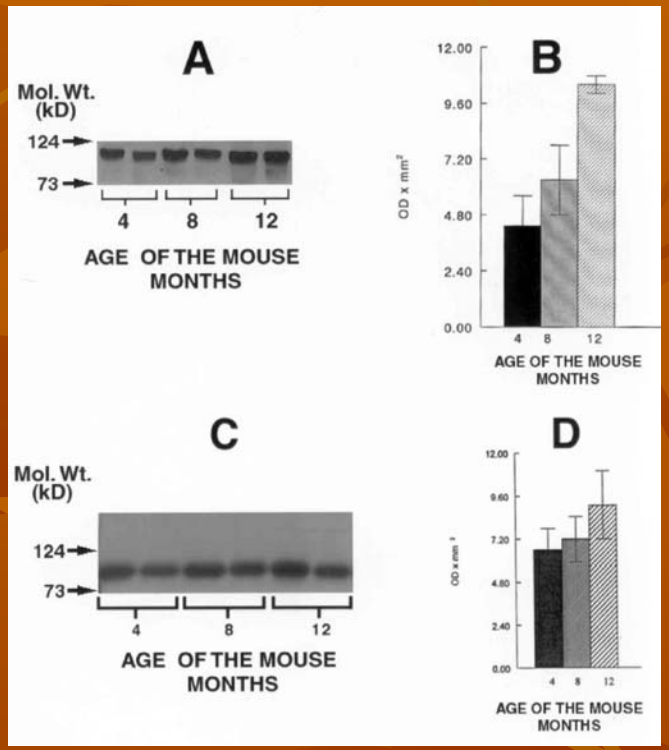


Increased Beta-amyloid in SAMP8 Mice

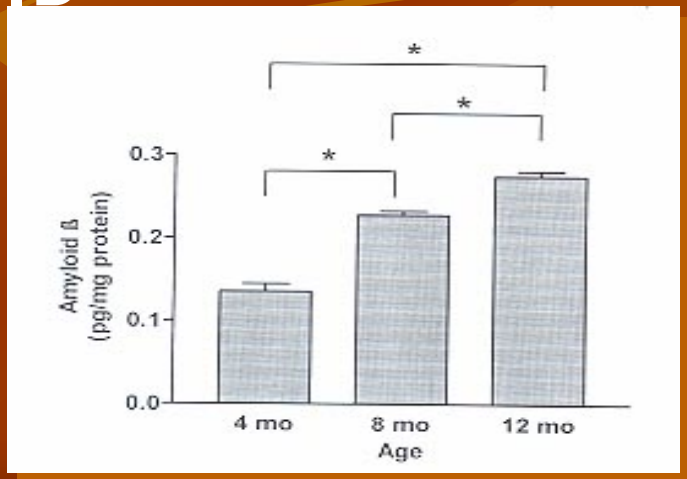
mRNA



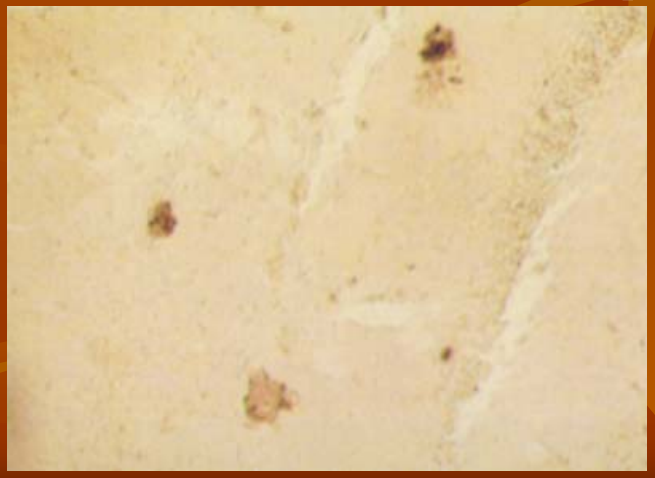
APP



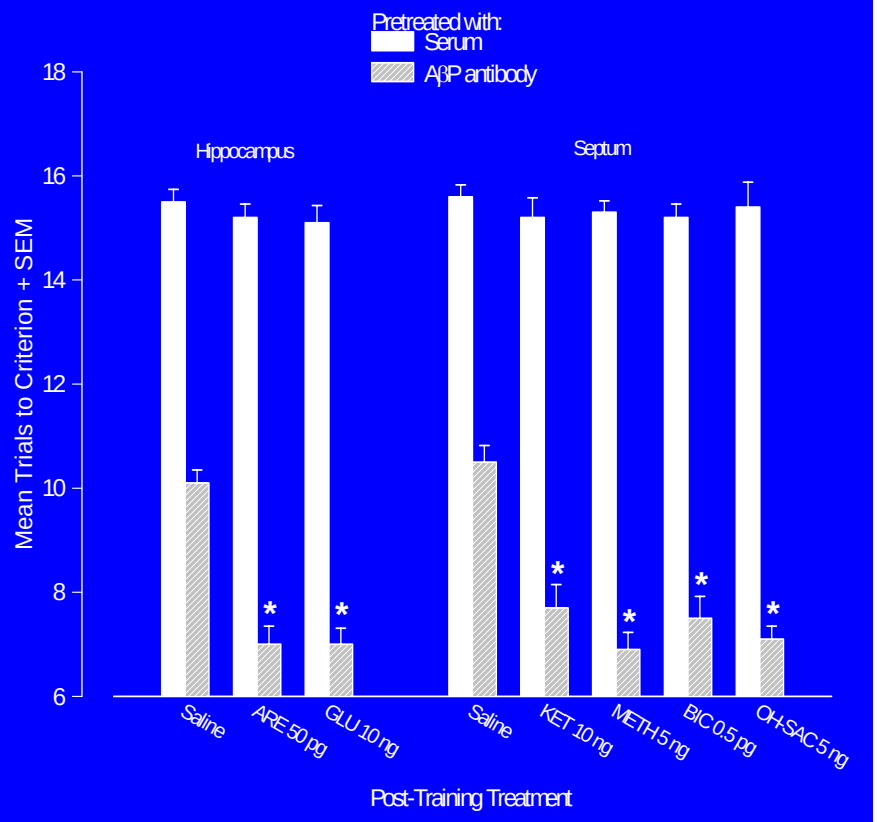
AMYLOID β

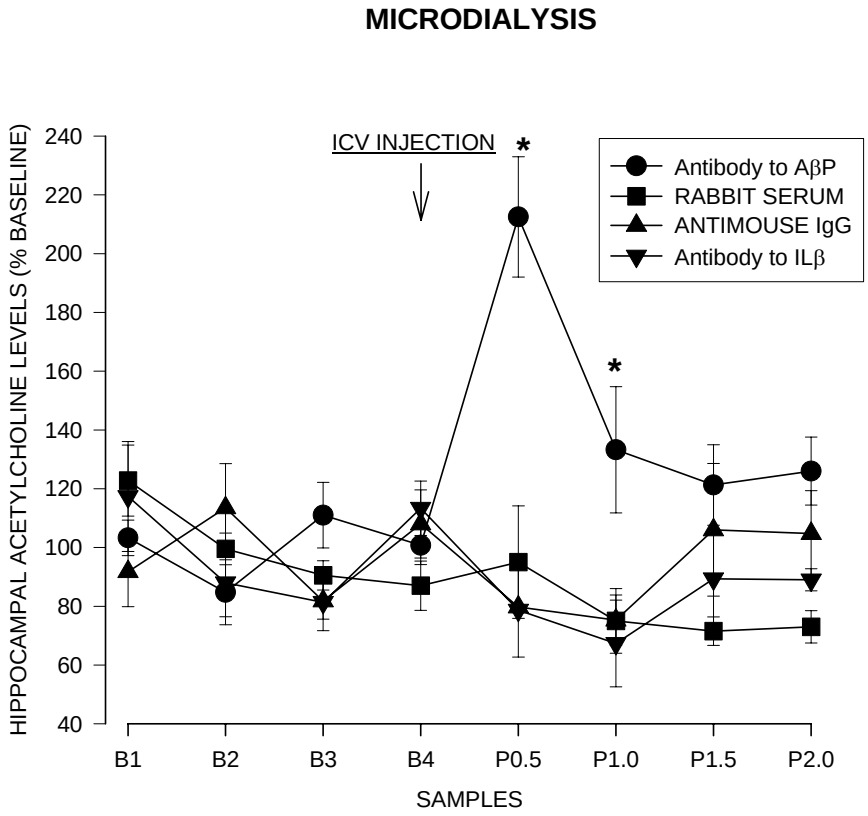


PLAQUE



Antibodies to β-Amyloid reverse memory deficit and increase acetylcholine

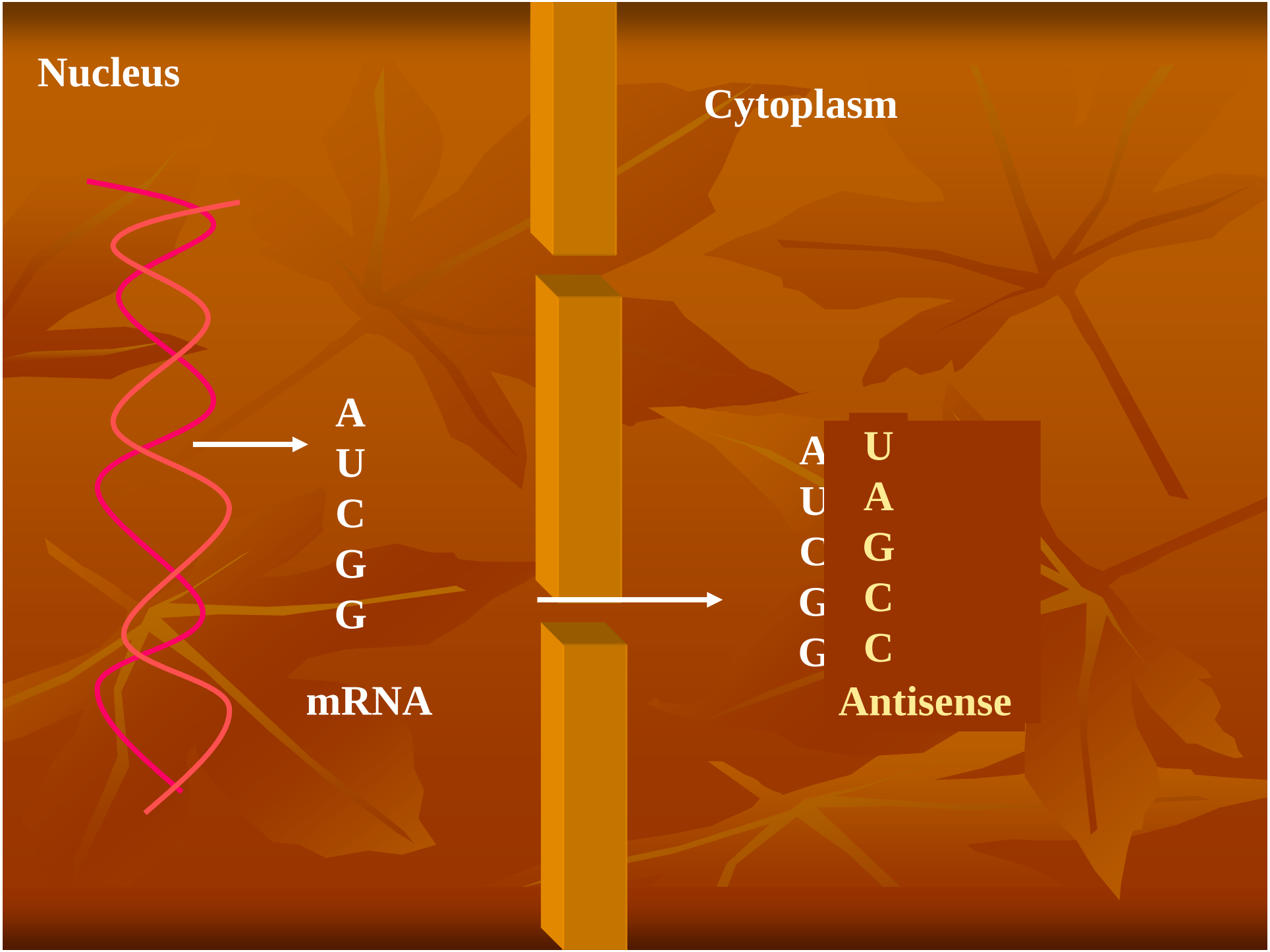




SAMP8 MICE

Comparison of Amino Acid Sequence Human, BALB/x and P8 Brain Amyloid βProtein.

	1	15	30	45
Human	DAEFRHDSGYQVHHQKLVFFAGDVGSNKGAIIGLMVGGVVIATVI			
(Balb C)	G F R		G	
Sam P8	G F R		N	
Impairing memory process	→ 17 – 22 ←			
Insoluble neurotoxic region	→25 - 35 ←			


Nucleus
Cytoplasm
A
U
C
G
G
mRNA
A U
U A
C G
G C
G C
Antisense

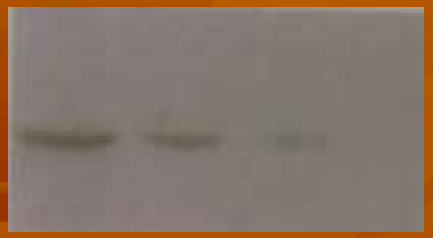
Development of Antisense

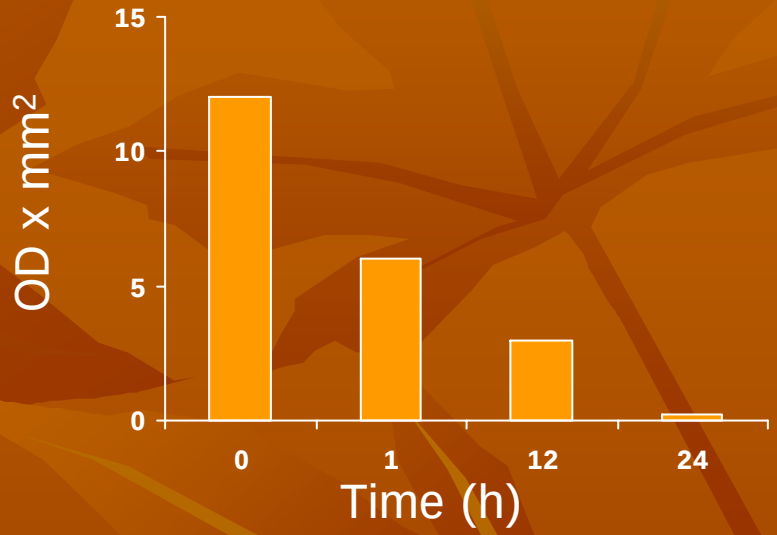
A phosphorothioate 42merAntisense Directed At mid region of AßP

- DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA - AßP
- 1 10 20 30 40
- OL-1 ggcgcctttgttcgaacccacatcttcagcaaagaacaccag (30-17)

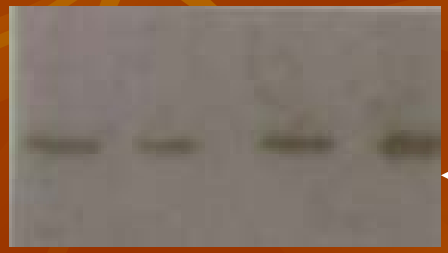
Neuroblastoma Cell Line

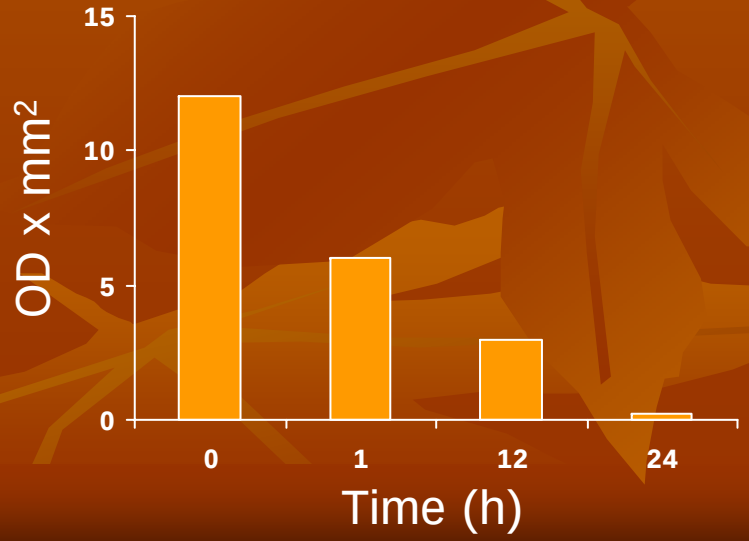
Antisense to Aβ





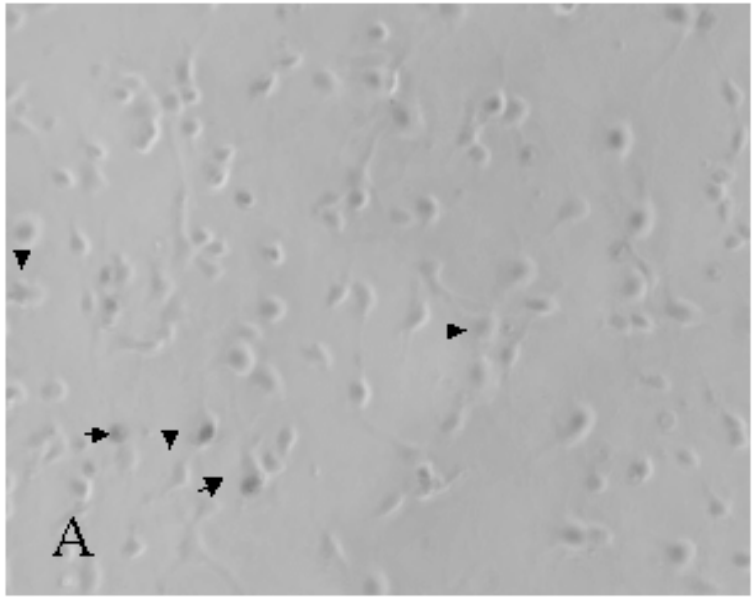
Random Antisense To Aβ

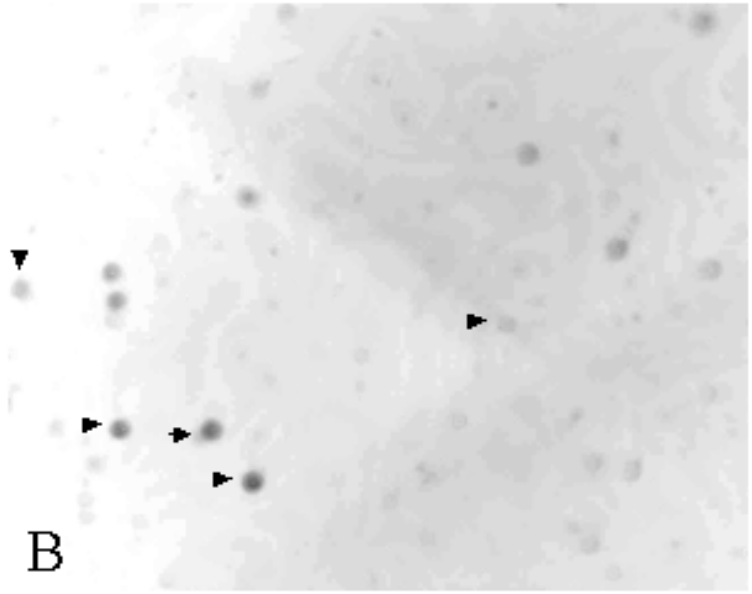




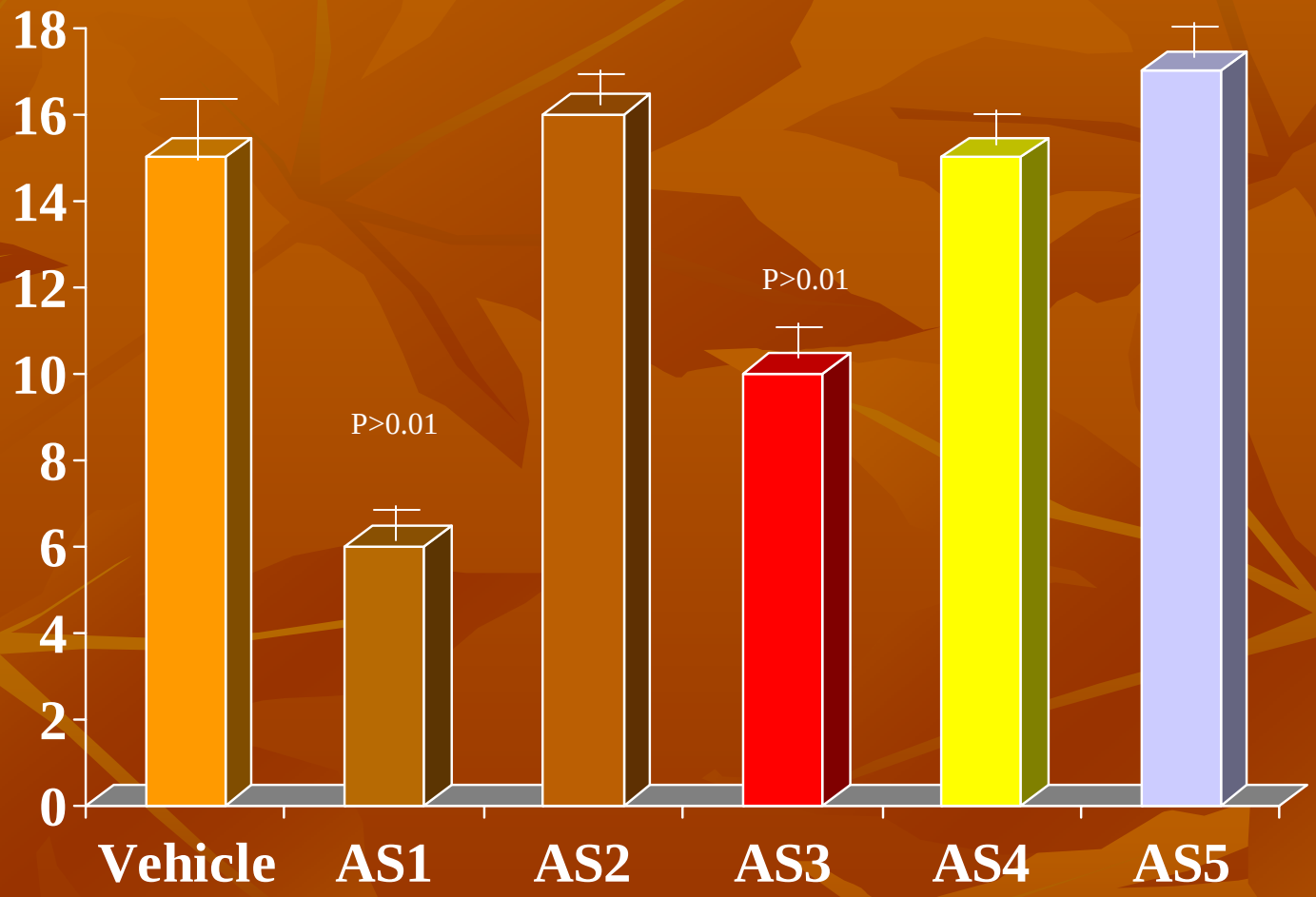
Phase Contrast of
Living Neurons

Fluorescence from 5’ –FITC-AO

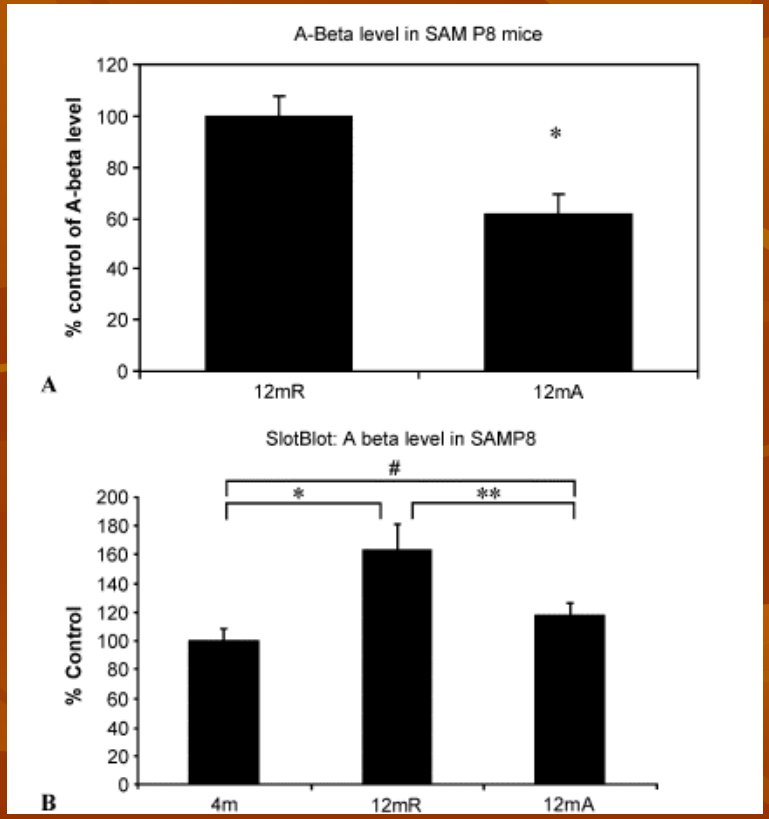




Retention T-Maze Footshock Avoidance 3 Weeks After Antisense Administration

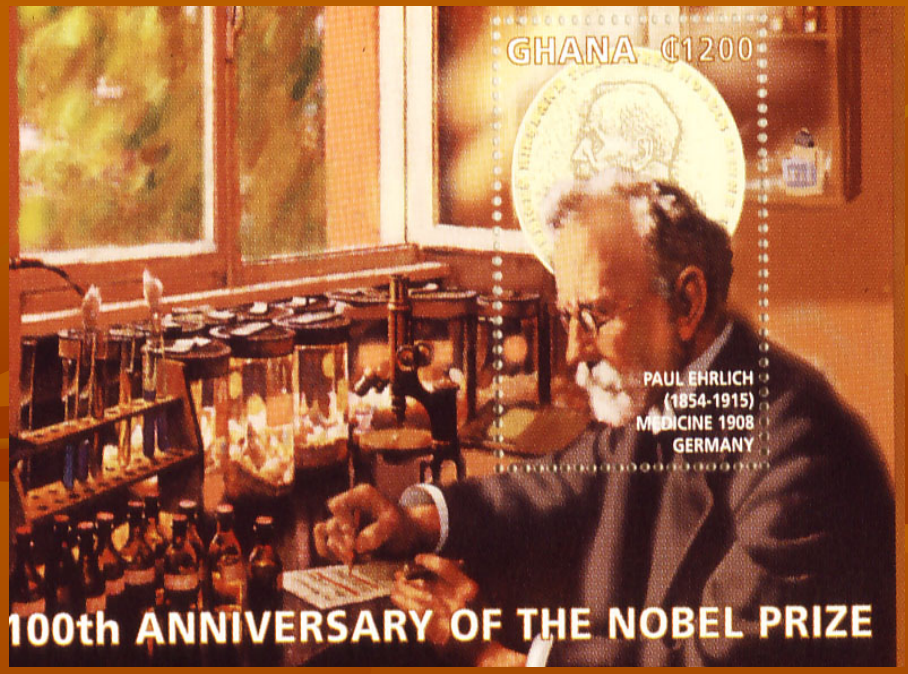


AO Treatment Decreases Aβ levels in Aged SAMP8 Mice Brain



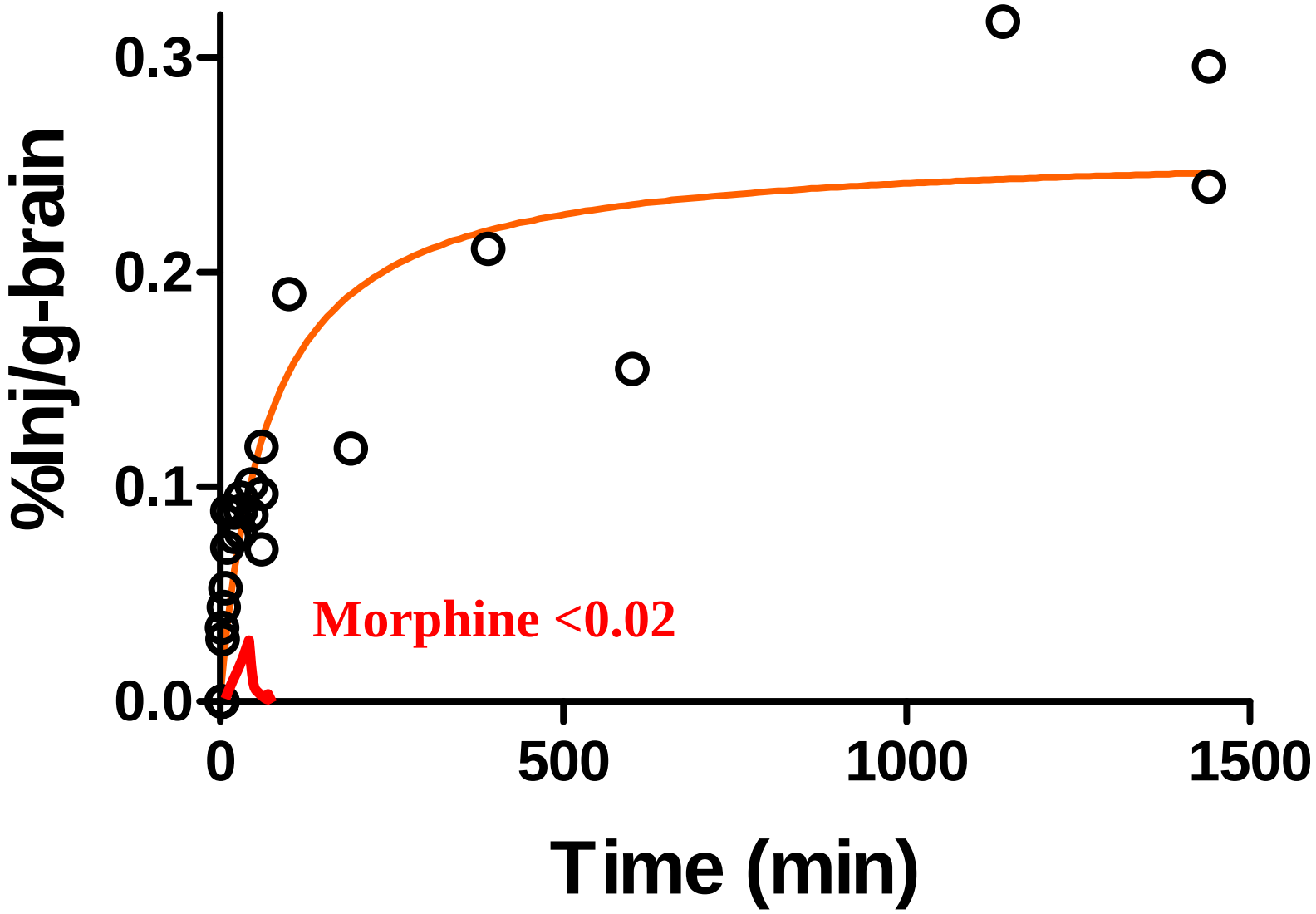
* p < 0.05, * p <0.05

Poon et al., 2004, Brain Res

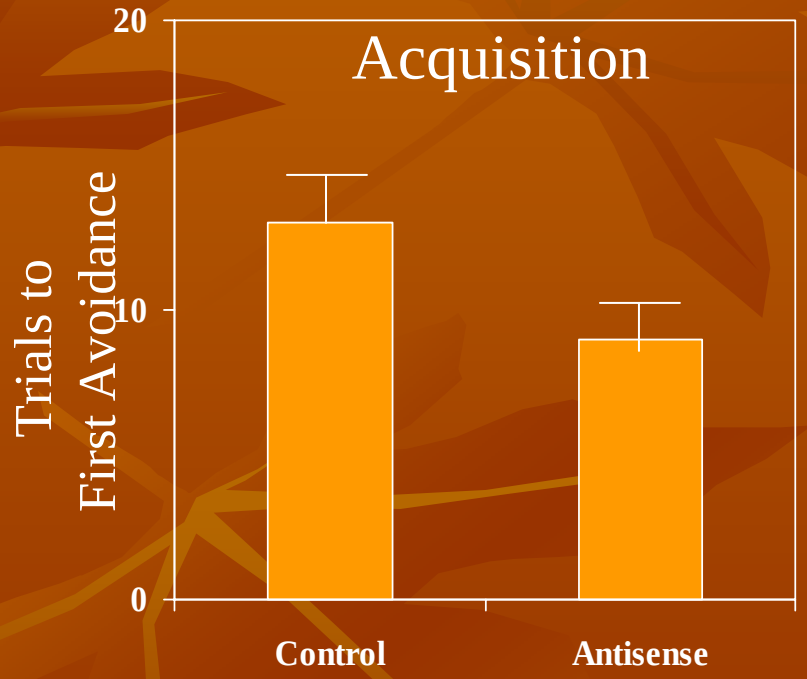


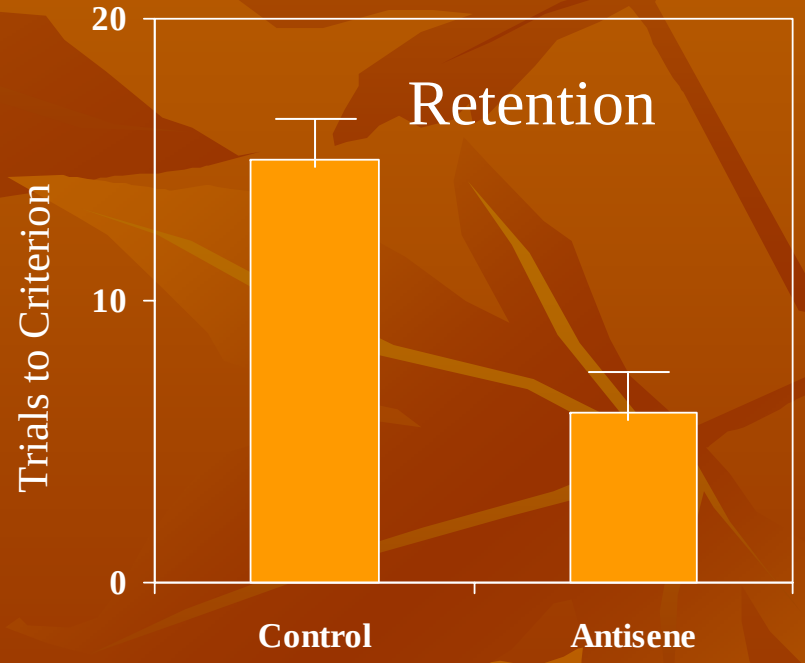
THE BLOOD BRAIN BARRIER

Antisense is transported across the BBB



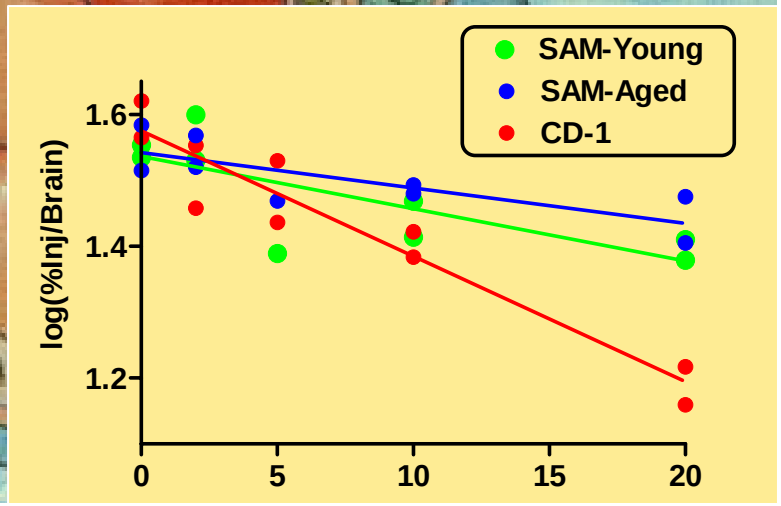
EFFECTS OF PERIPHERAL OTS-1



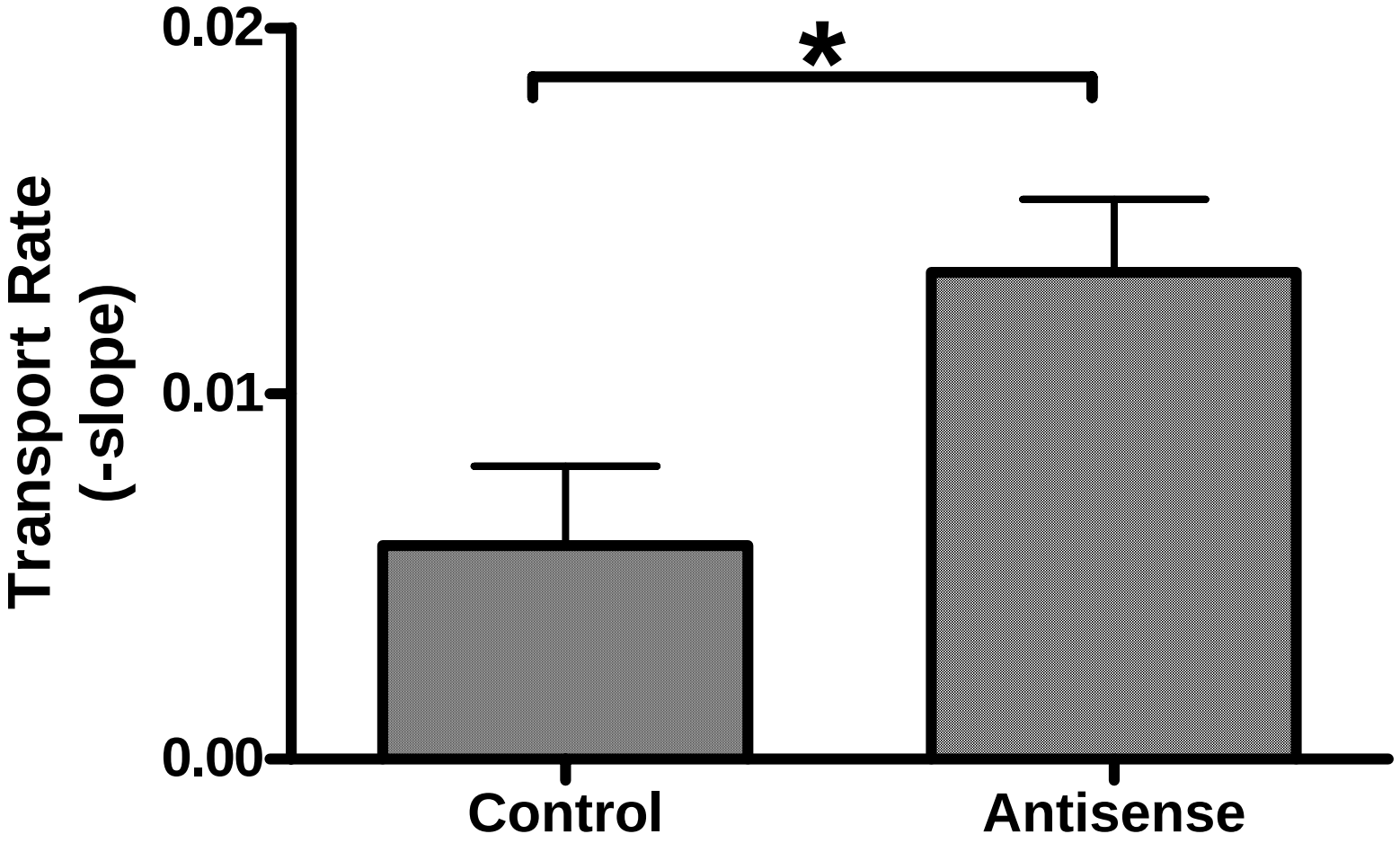


Brain to Blood Efflux of Amyloid Beta Peptide

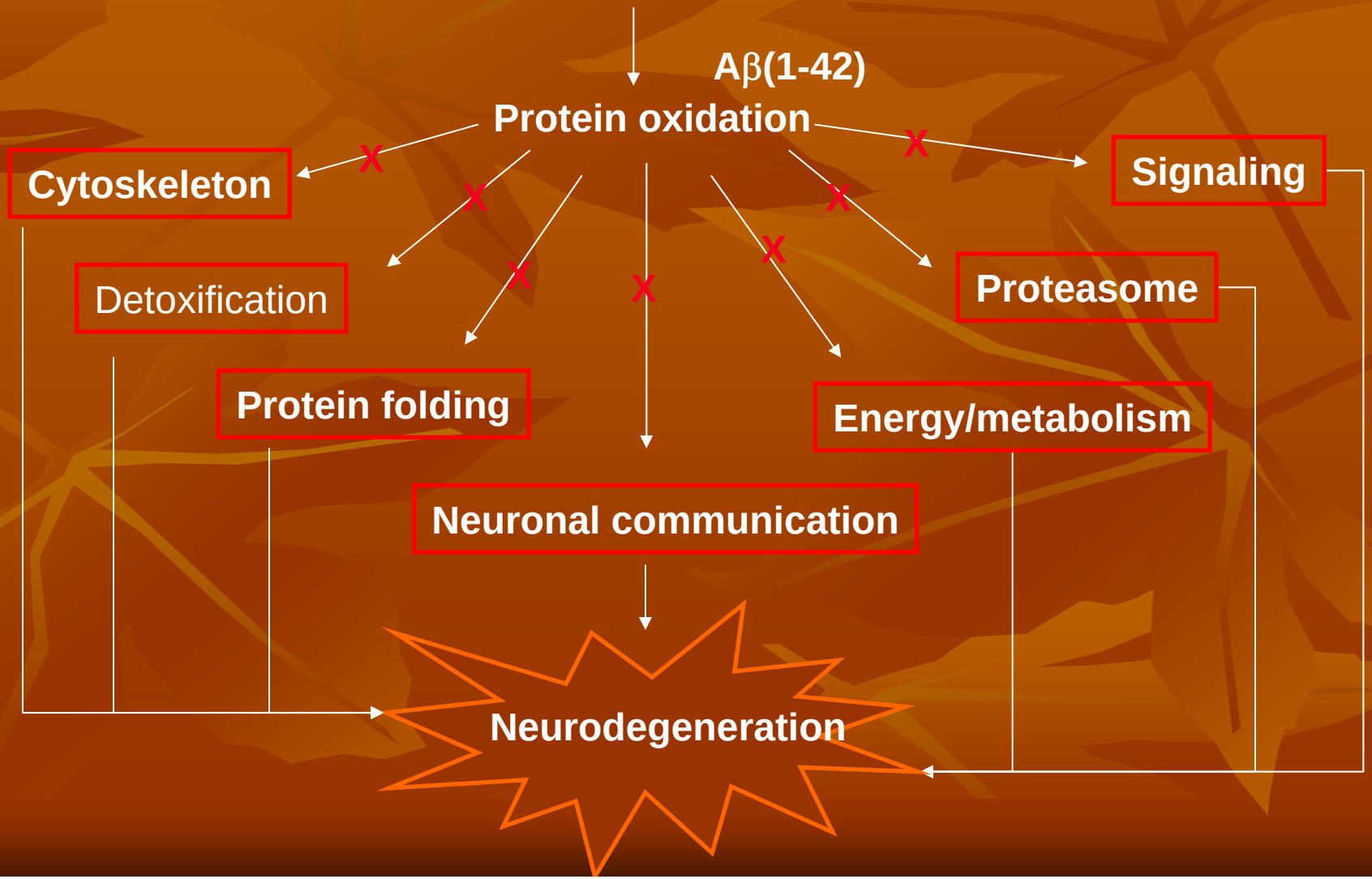
There is slowed efflux in Alzheimer Disease



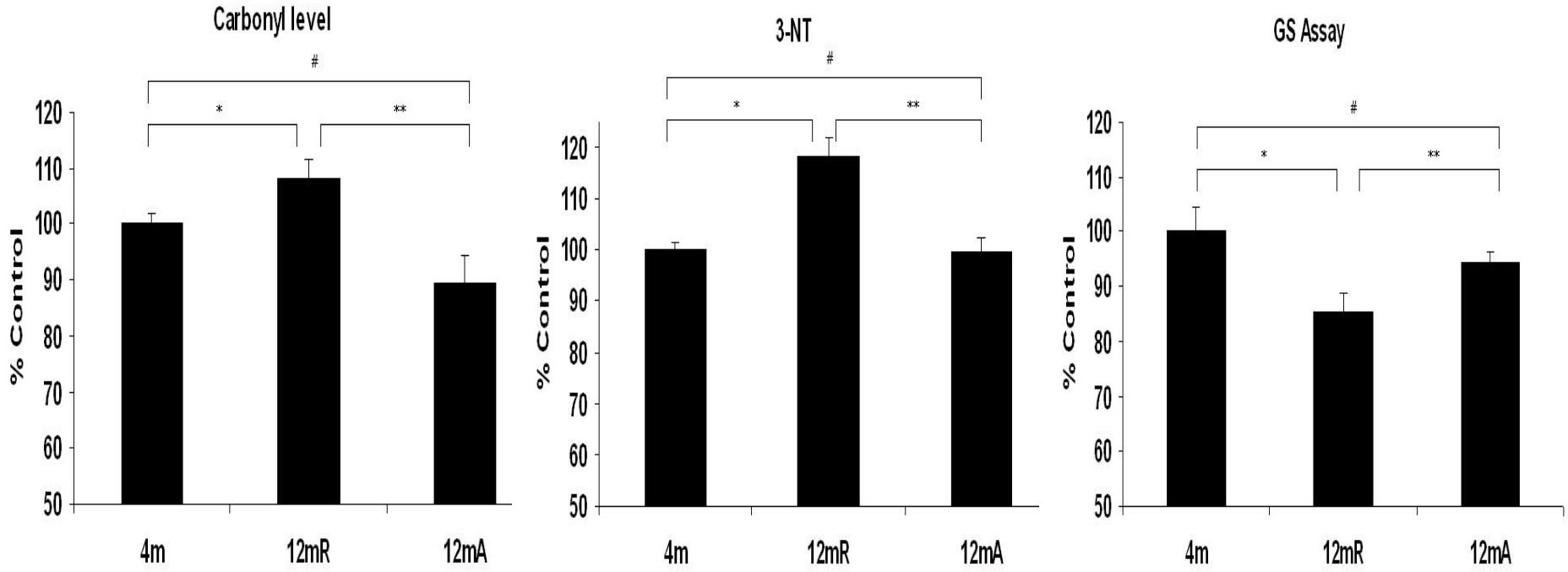
Antisense reverses the BBB transport defect



Potential Dysfunction of Proteomics-Identified, Aβ(1-42)-Induced Oxidized Proteins: Neurotoxicity That is Similar to That in AD Brain



AO Treatment Decreases Protein Oxidation in Aged SAMP8 Mice Brain

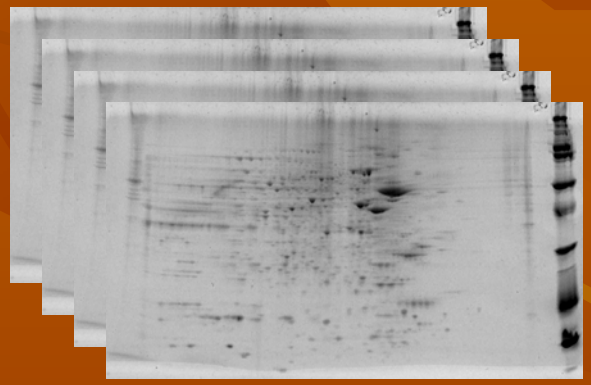


* p < 0.05, ** p < 0.05

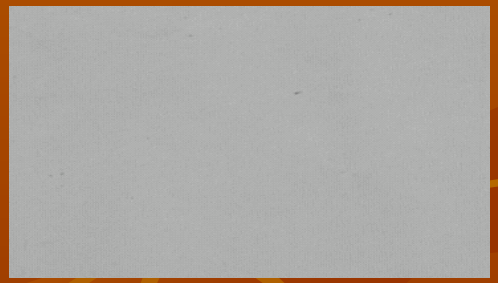
Poon et al., 2004, Brain Res

Detection and Image Analysis

Sypro Staining



Average protein level for each spot

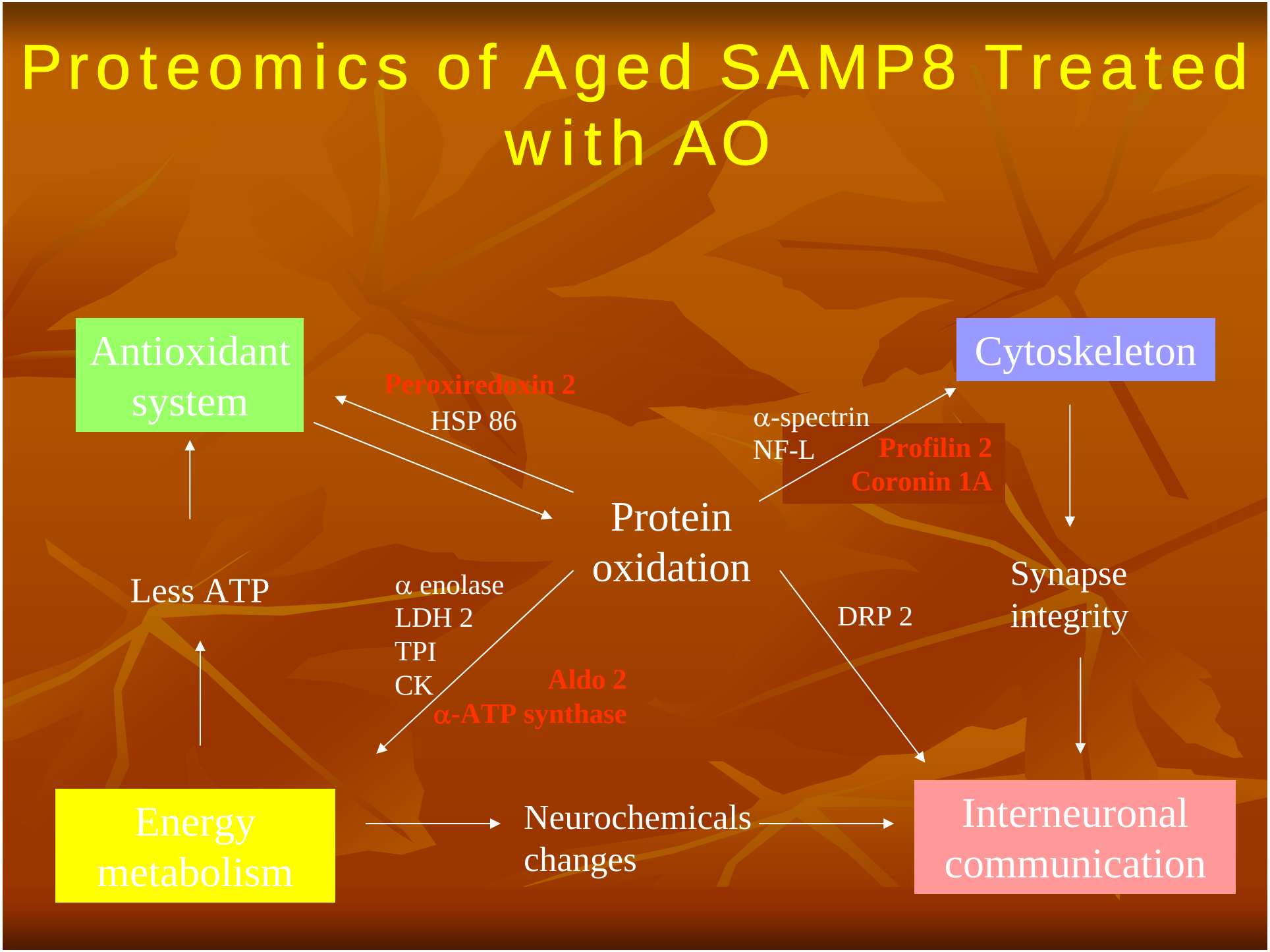


Average Specific Carbonyl level for each spot

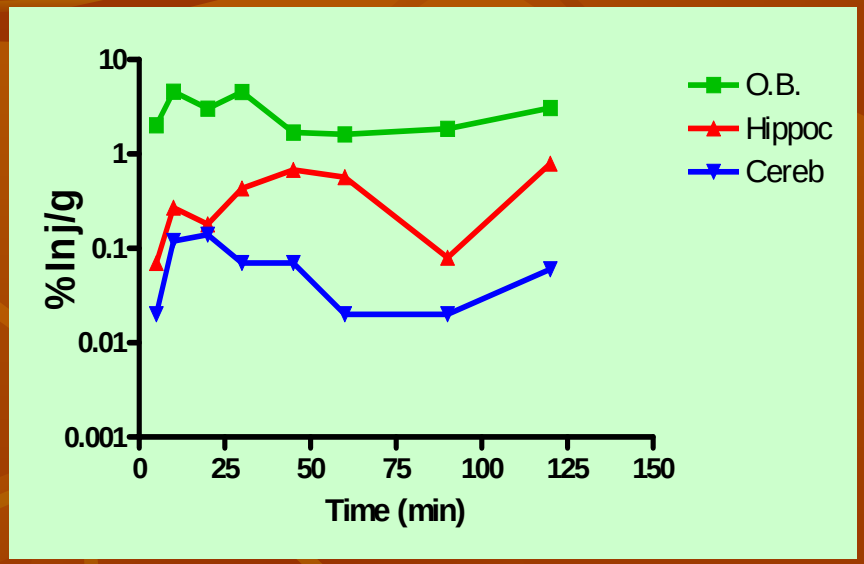
Western Blotting

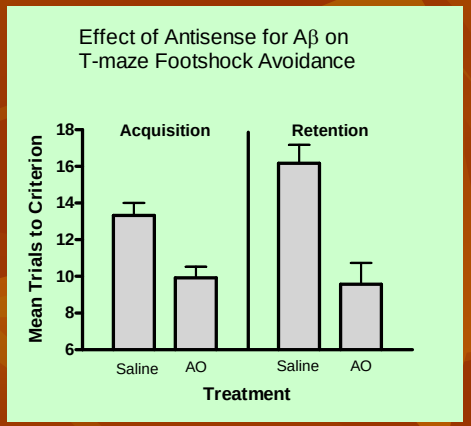
Statistical Analysis

Proteomics of Aged SAMP8 Treated with AO



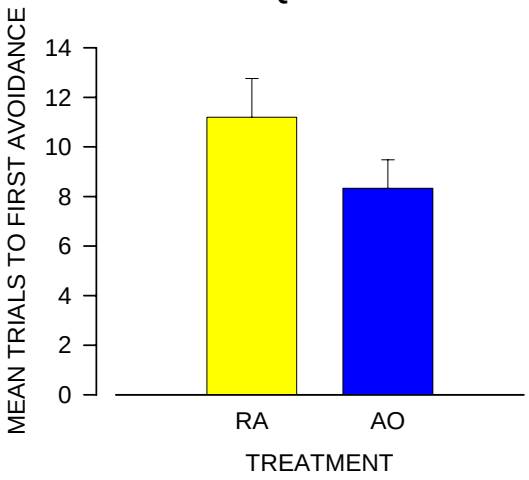
NASAL ADMINISTRATION



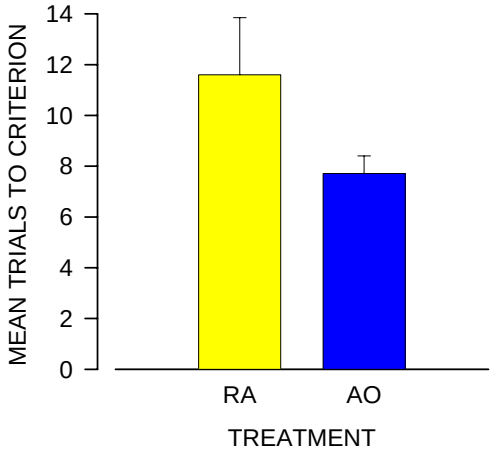


APPSWE (13-15 MONTHS OF AGE)
T-MAZE FOOTSHOCK AVOIDANCE

ACQUISITION



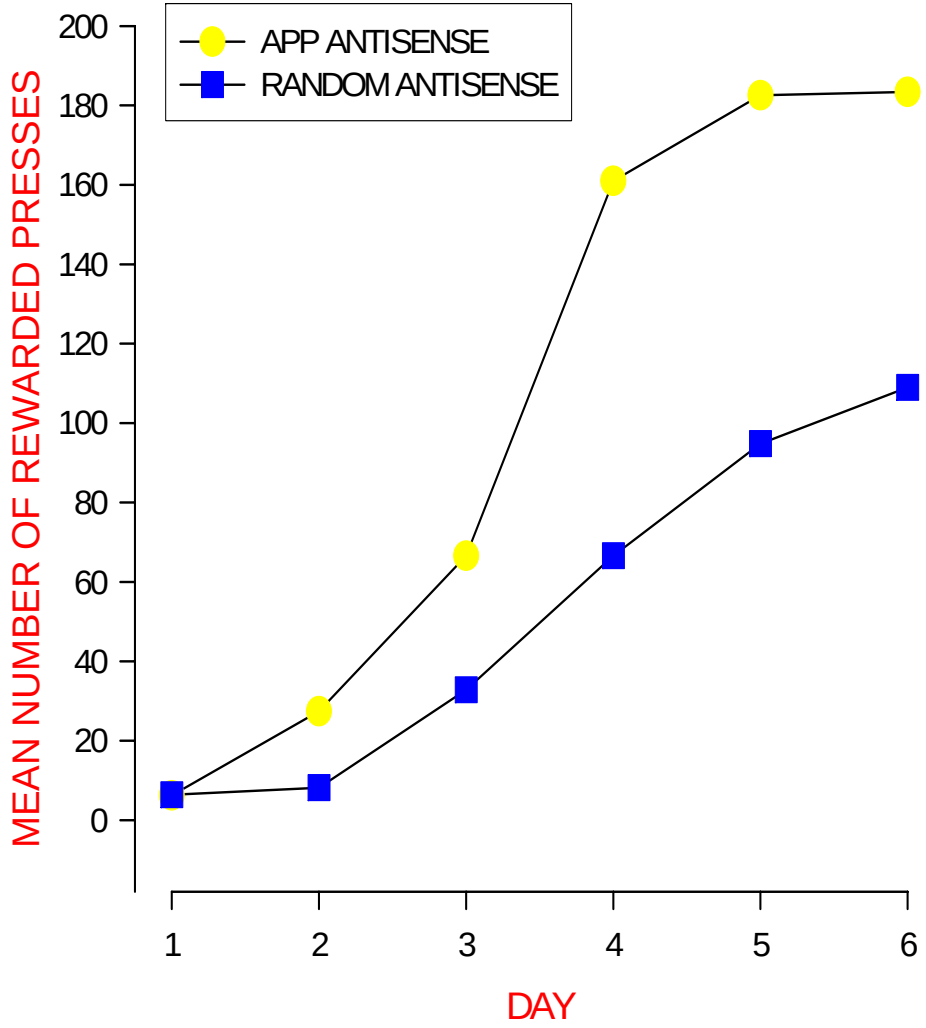
RETENTION



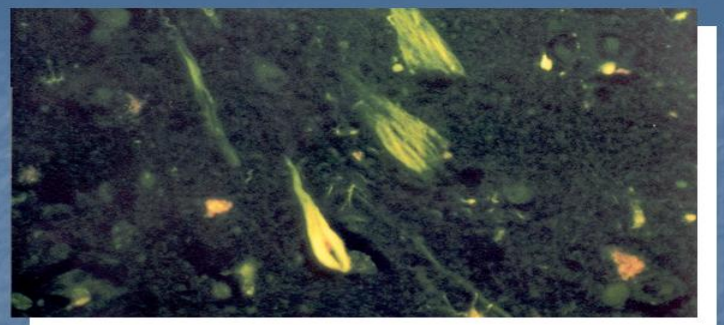
RA = RANDOM ANTISENSE

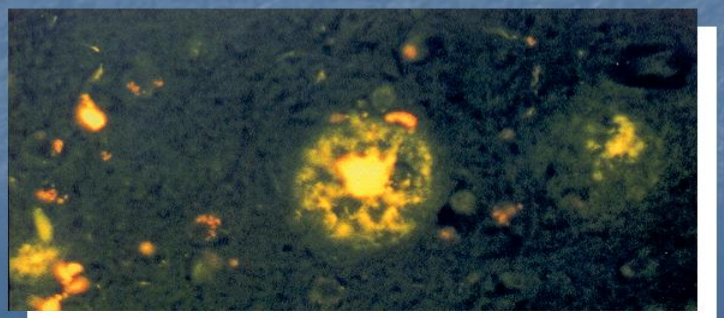
AO = APP ANTISENSE

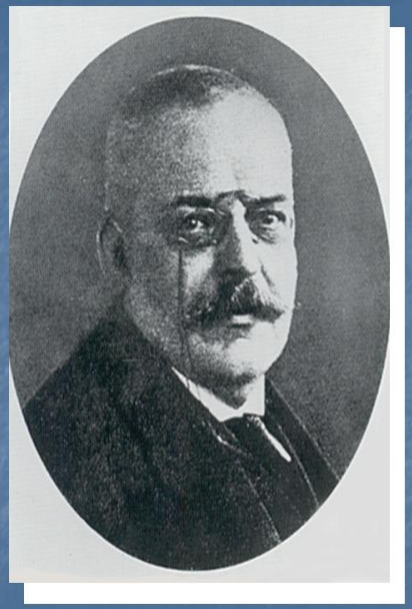
LEVER PRESS
APPSWE



Antisense to APP reverses memory deficits, oxidative damage and delayed AB clearance in mice models of Alzheimer's disease. It can be administered intranasally.







Alois Alzheimer

What is the physiological role of amyloid beta protein?

Low doses of Amyloid Beta Protein Enhance Memory

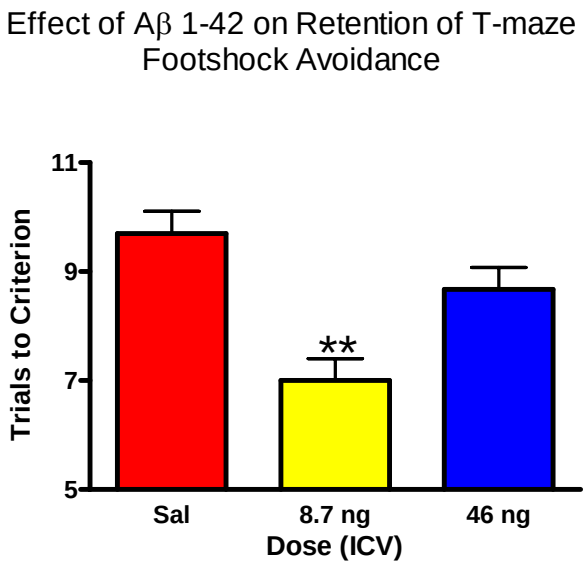


Figure 5. Low doses of Aβ 1-42 administered ICV immediately after training improves retention in T-maze footshock avoidance. The ** indicates P<0.01.

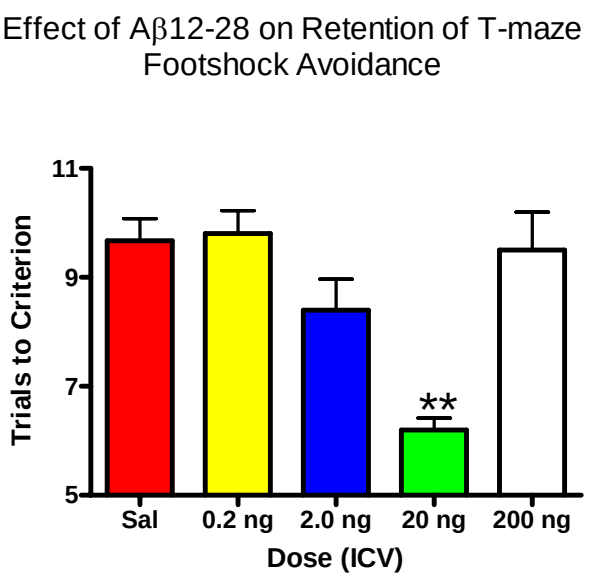


Figure 4. Low doses of Aβ 12-28 administed ICV immediately after training improves retention in T-maze footshock avoidance. The ** indicates P<0.01.

Inhibition of Amyloid Beta Protein inhibits learning in young animals

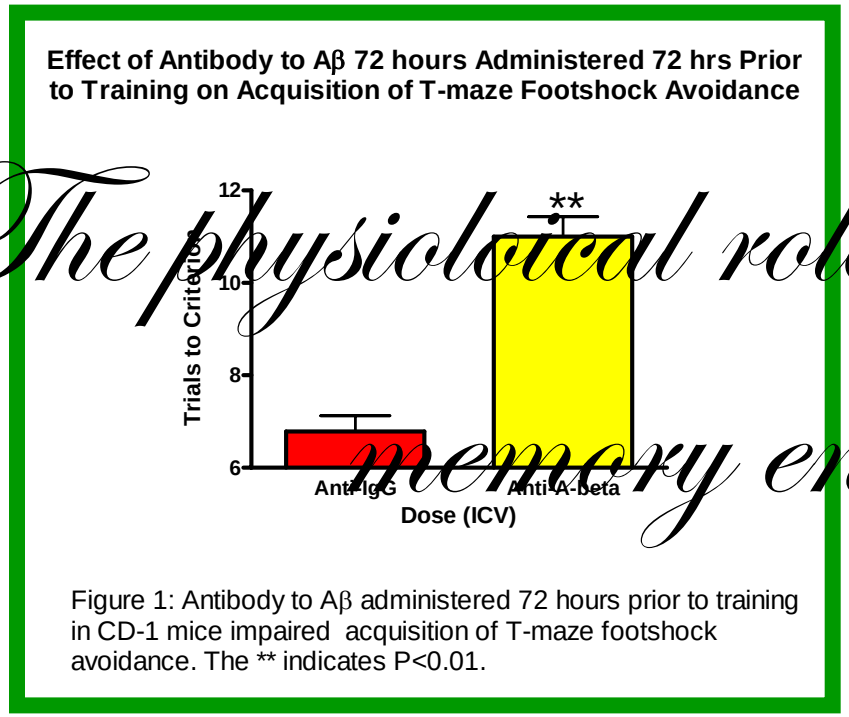


Figure 1: Antibody to Aβ administered 72 hours prior to training in CD-1 mice impaired acquisition of T-maze footshock avoidance. The ** indicates P<0.01.

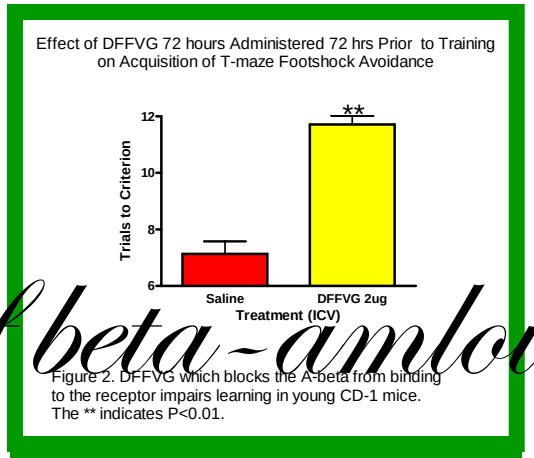


Figure 2. DFFVG which blocks the A-beta from binding to the receptor impairs learning in young CD-1 mice. The ** indicates P<0.01.

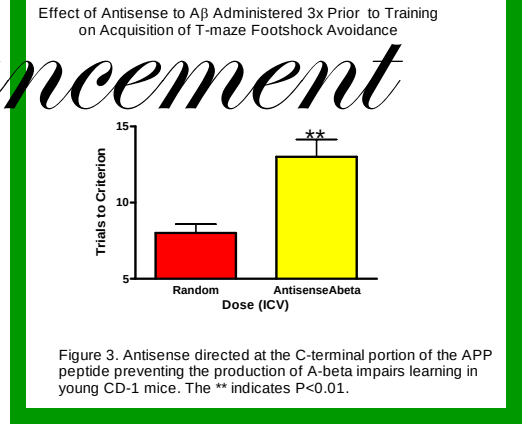
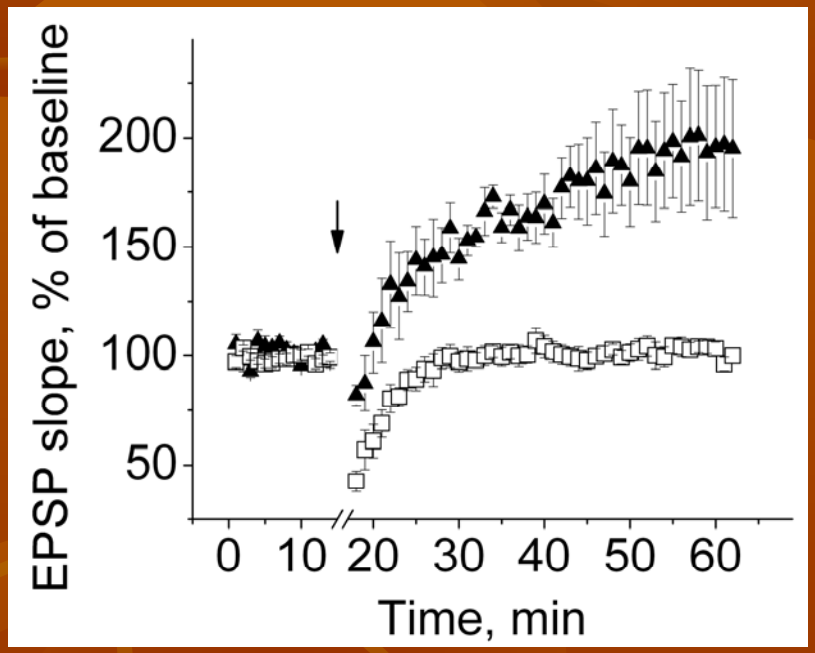


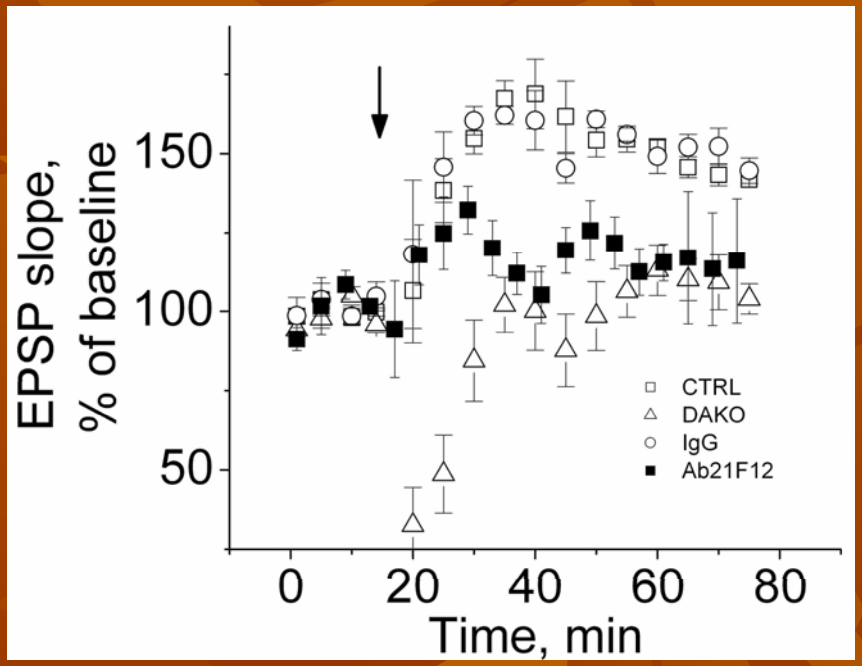
Figure 3. Antisense directed at the C-terminal portion of the APP peptide preventing the production of A-beta impairs learning in young CD-1 mice. The ** indicates P<0.01.

The physiological role of beta-amloid is memory enhancement

Long Term Potentiation



DFFVG

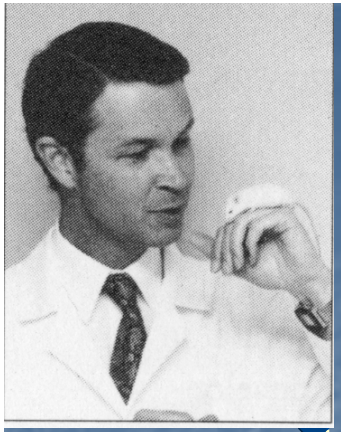


Amyloid β antibodies

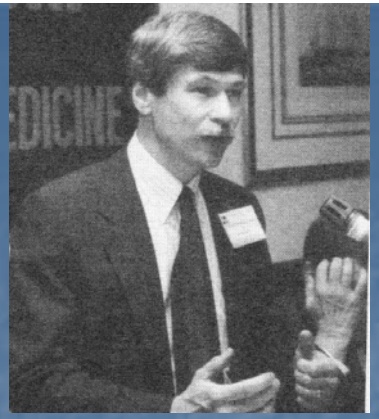
Hormesis and Memory Conclusions

All (?) memory enhancing agents follow the laws of hormesis.

Low doses of amyloid β peptide the putative causative agent of Alzheimer's disease enhance memory



MEMORIES



Flaherty

Banks

Butterfield

Tumosa

James Flood

Farr

Tariq

Kumar

Fai Poon

St. Christopher's House