Insulin Resistance and Alzheimer's Disease: A Novel Therapeutic Target

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Overview

- Insulin plays a role in cognition and normal brain function
- Dysregulation of insulin increases risk for AD and other neurodegenerative diseases
- Potential mechanisms of increased risk: Effects on inflammation and β-amyloid
- Therapeutic applications: Effects of treating insulin resistance and normalzing CNS insulin

Insulin and the Brain

- Insulin crosses BBB via saturable receptor-mediated trancytosis (Banks et al, 97)
- Insulin receptors have synaptic localization in hippocampus and throughout cortex (Apelt et al, 2001)
- Increases glucose utilization in specific brain regions (Bingham et al, 2002)
- Increases levels of dopamine, acetylcholine, norepinephrine (Figlewicz et al, 1993)
- Modulates membrane potentials, membrane expression of NMDA receptors, and neuronal firing/LTP in hippocampus and EC (Skeberdis et al, 2001)
- Enhances memory at optimal dose

Chronic Effects of Insulin: Too Much of a Good Thing

- Insulin typically secreted and cleared quickly
- High, chronic elevations problematic
  - ➔ Reduced brain insulin uptake (Schwartz et al, 1990; Stein et al, 1987)
  - ➔ Reduced neurotransmitter levels
  - ➔ Reduced glucose utilization (periphery and CNS?)
  - ➔ Memory impairment

Insulin Resistance and Alzheimer's Disease

- Insulin resistance/hyperinsulinemia increase risk of AD and memory impairment (Ott et al, 1999; Peila et al, 2002; Luchsinger et al, 2004)
- Risk increases with age (Ryan et al, 2001)
- Insulin resistance a particular risk factor for AD patients without the APOE-e4 allele (Kuusisto et al, 97; Liotsa et al, 02; Craft et al, 03)
- Insulin may modulate risk in part through effects on Aβ42
  - ➔ Modulates Aβ42 levels in vitro
  - ➔ Enhances release, regulates degradation by IDE (Gasparini et al, 2001; Qiu et al, 2001; Zhao et al, 2004)

Does Insulin Affect CNS Levels of Aβ?

- Will insulin administration raise Aβ42 levels in CSF, consistent with *in vitro* effects of insulin on Aβ release & degradation?
- Will effects differ according to age?
- Will results be related to changes in biomarkers associated with inflammation?

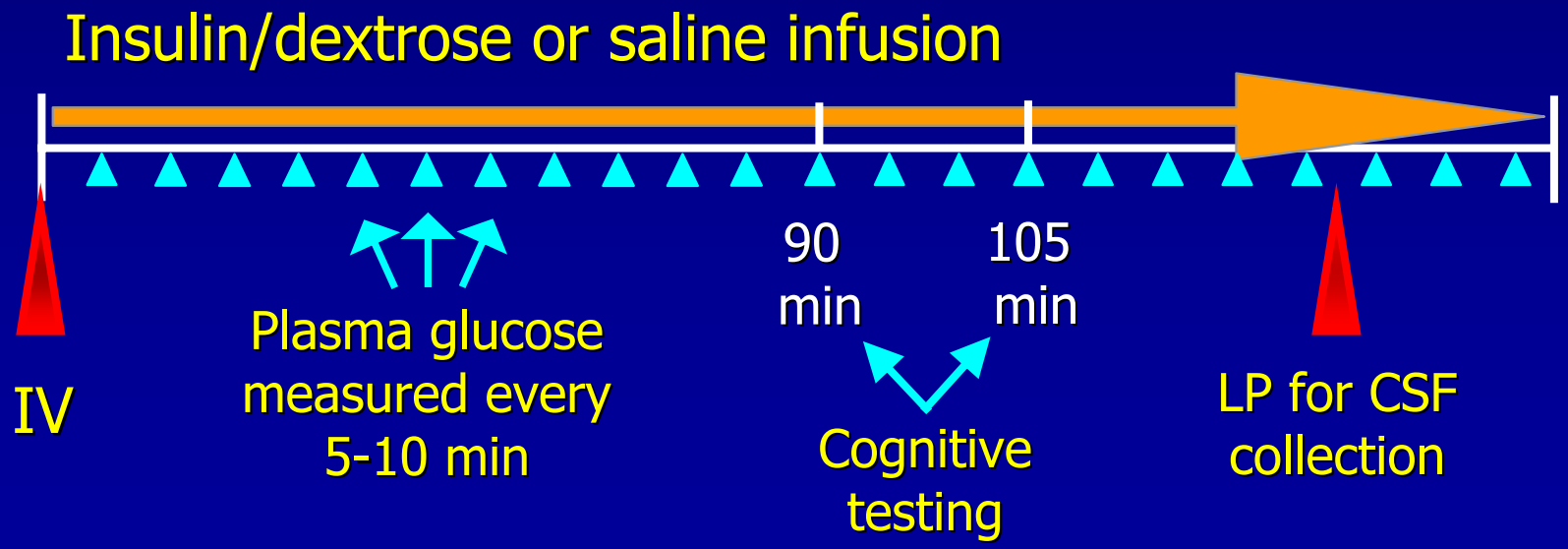
Methods

Fasted Subjects (n=16, mean age = 68.7)

Separate days, counterbalanced order

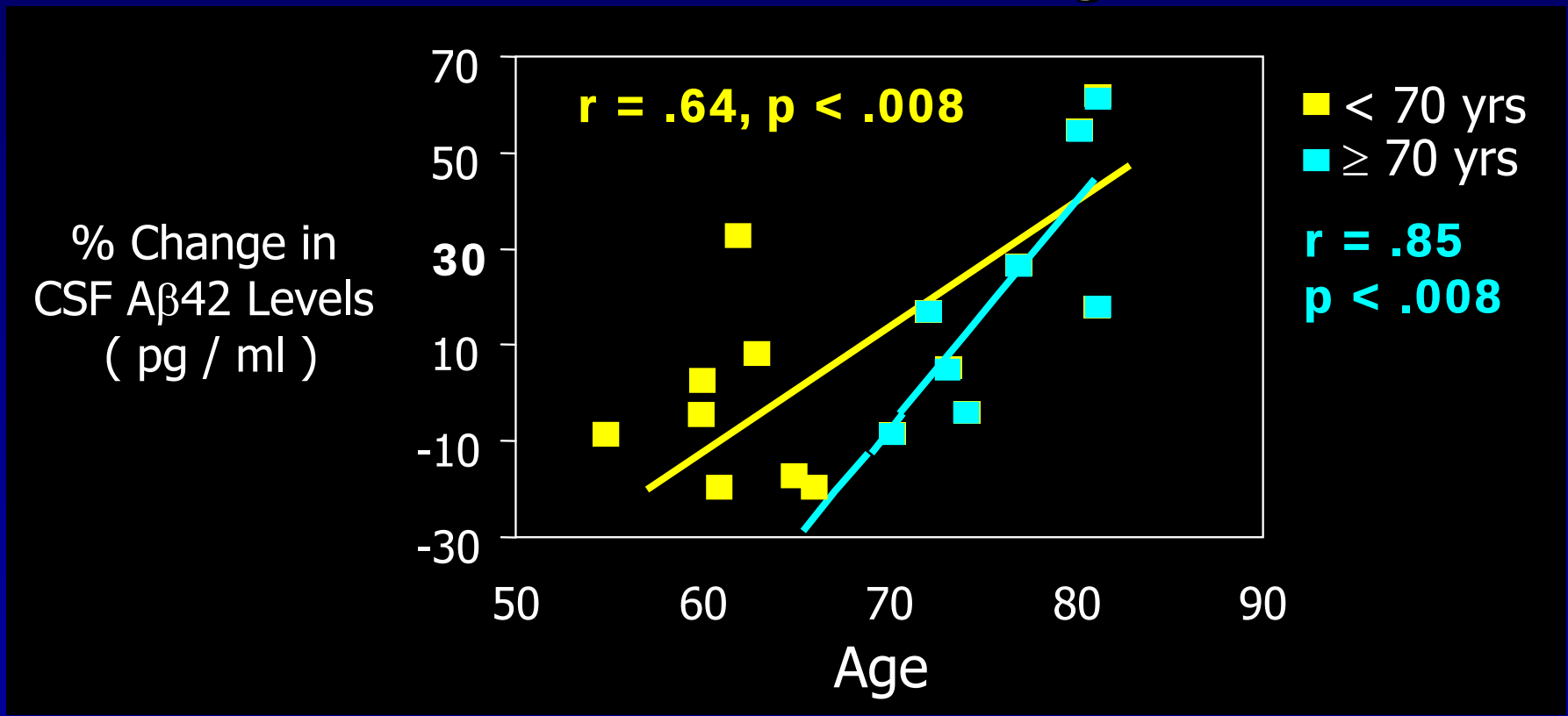
Saline

Insulin (85 μU/ml)
Dextrose (95 mg/dl)



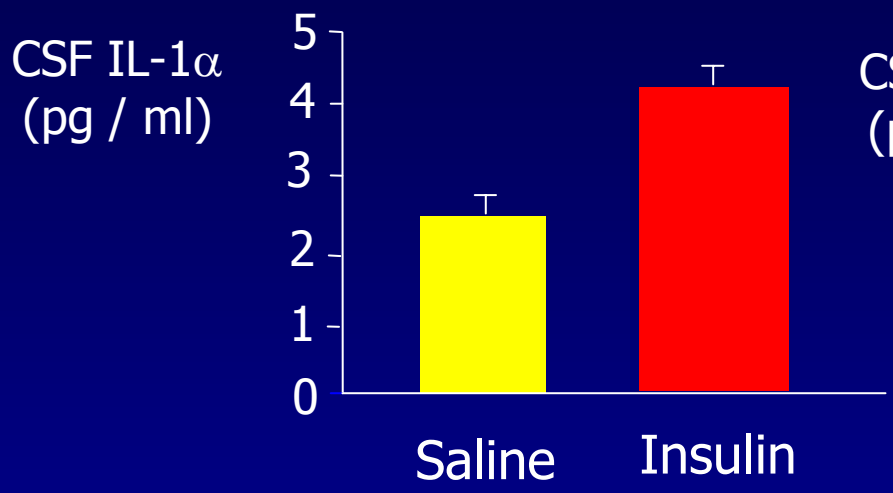
Effects of Insulin on CSF Aß42 Levels in Normal Older Adults: Results

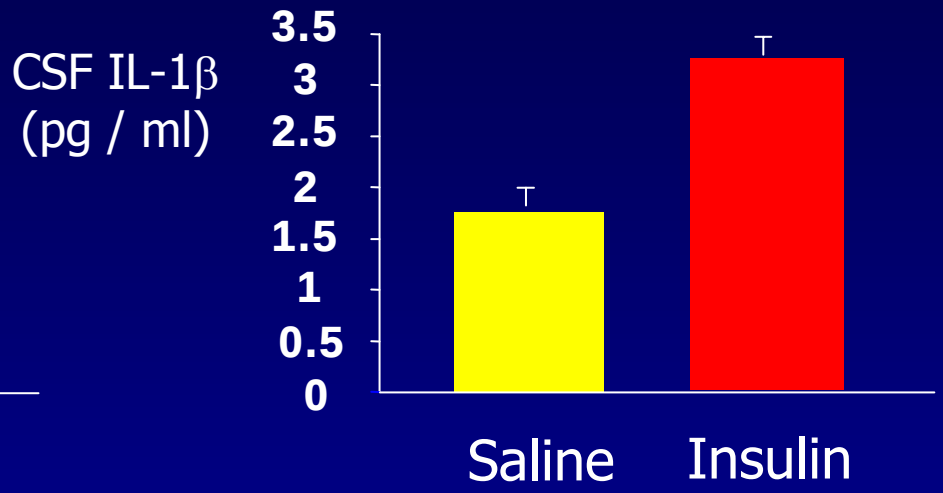
Insulin-induced change in Aβ42 is correlated with age

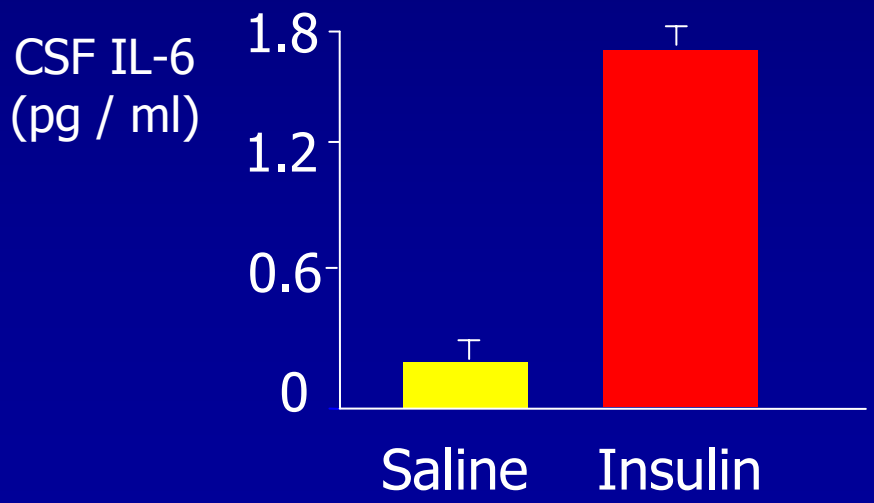


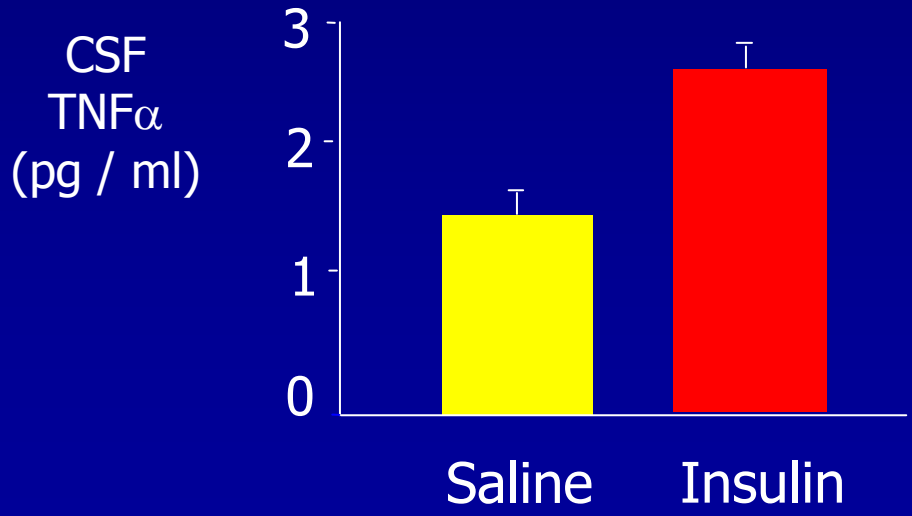
Watson GS, et al. *Neurology* 2003;60(12):1899-903

Results *Cytokines*







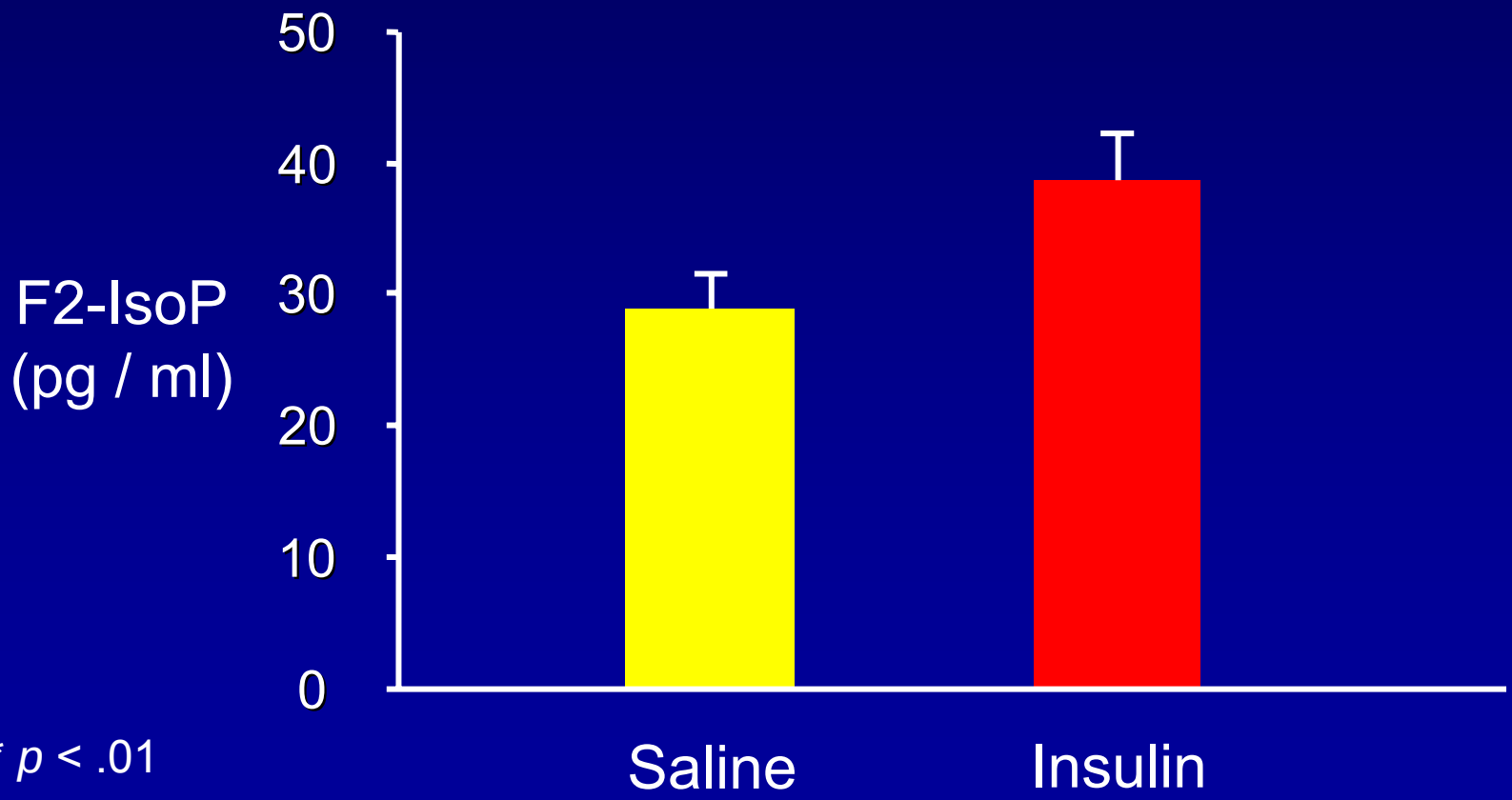


*p-values < .0001-.002 Fishel et al. *Neurology*, 2005

Results

CSF F2-IsoP

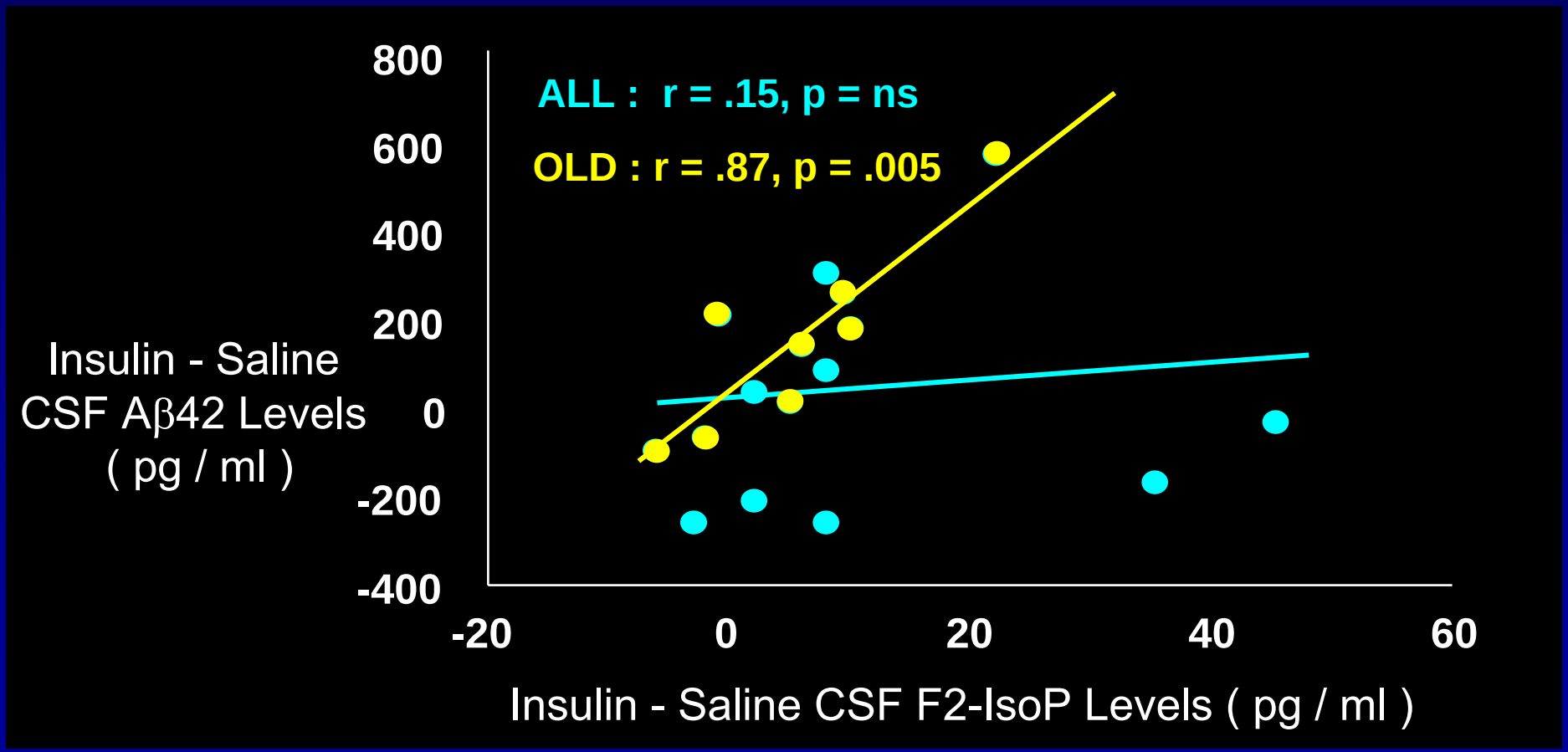
CSF F2-Isoprostane levels increase in response to insulin



* $p < .01$

Results

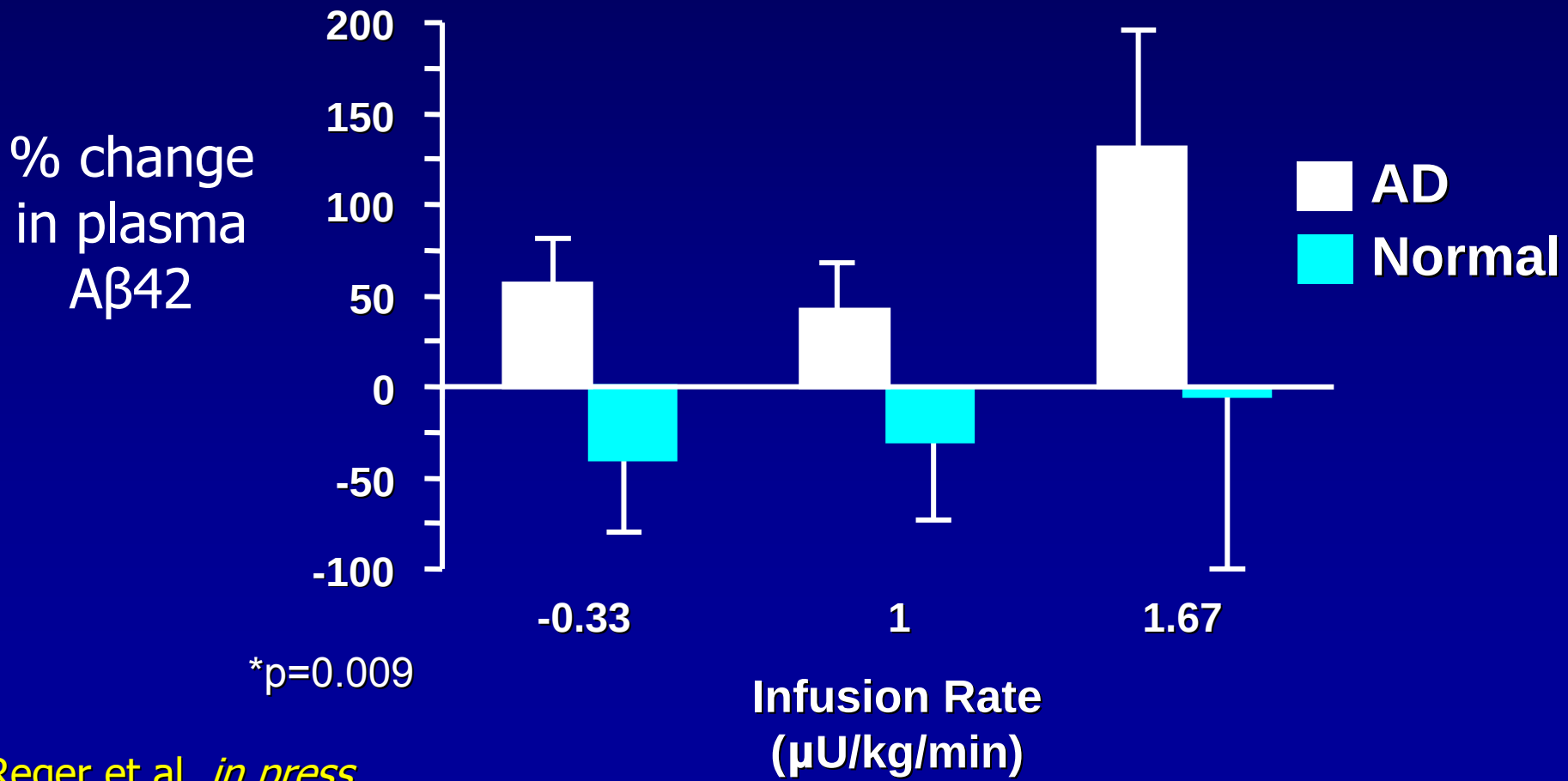
Insulin-induced change in CSF Aβ42 is correlated with F2-Isoprostane levels for the OLDER normal adults



Does insulin have similar role in Aβ regulation in periphery?

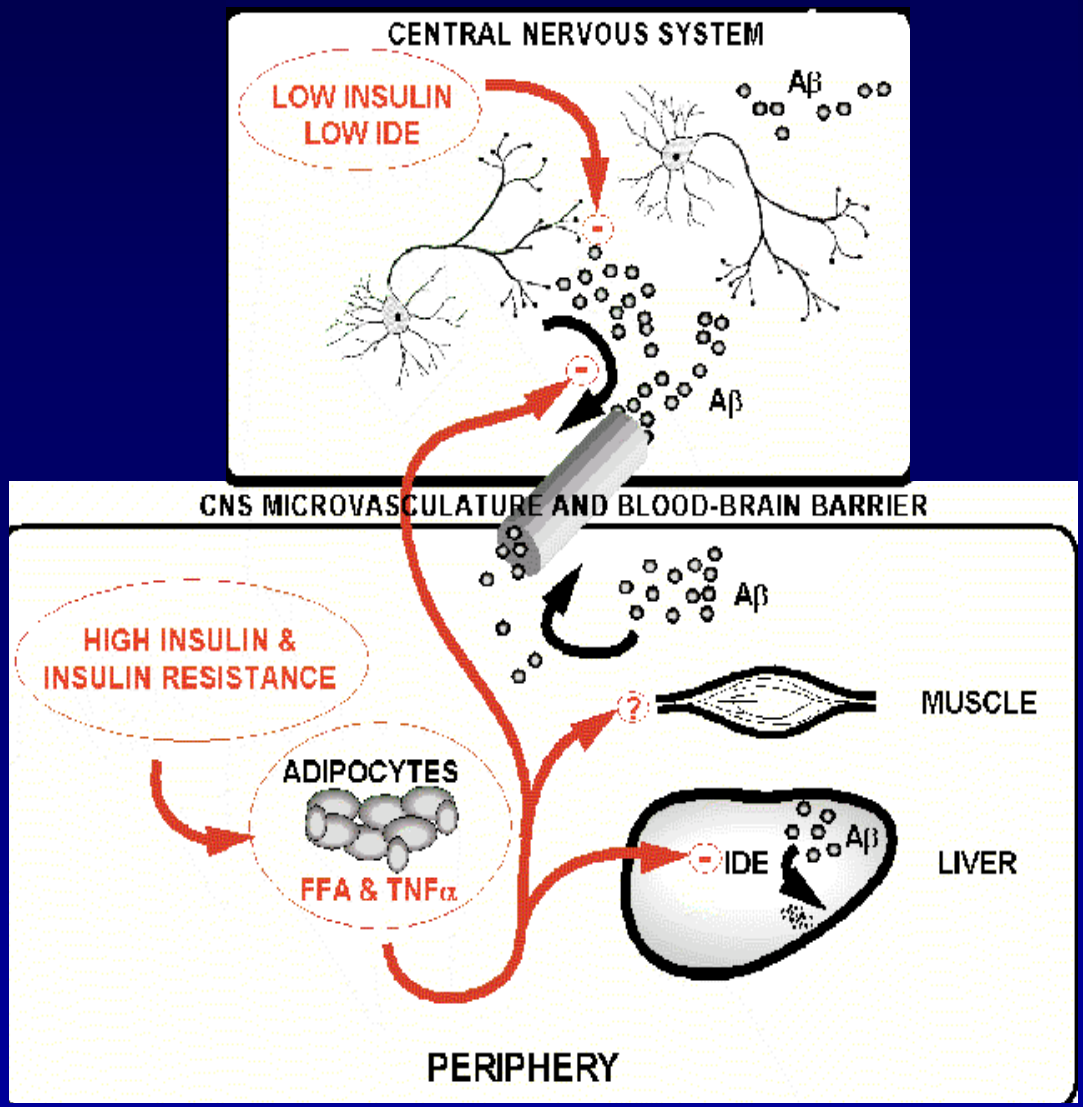
- Aβ cleared in liver and other peripheral sites (Ghiso et al 04)
- Plasma Aβ elevated for some AD patients, declines with progression (Mayeux et al. 03; Ertekin-Taner et al. 04)
- Aβ transported between periphery and brain (Mackic et al. 02; DeMattos et al. 02)
- IGF-1 and insulin increase levels of carrier proteins that bind Aβ and regulate its transport (Carro et al. 02)
- High plasma Aβ may obstruct clearance from or increase transport into brain

Dose-response effects of intravenous insulin on plasma Aβ42



Reger et al. *in press*

Model of Peripheral Insulin Resistance & Hyperinsulinemia Effects on Aβ Regulation

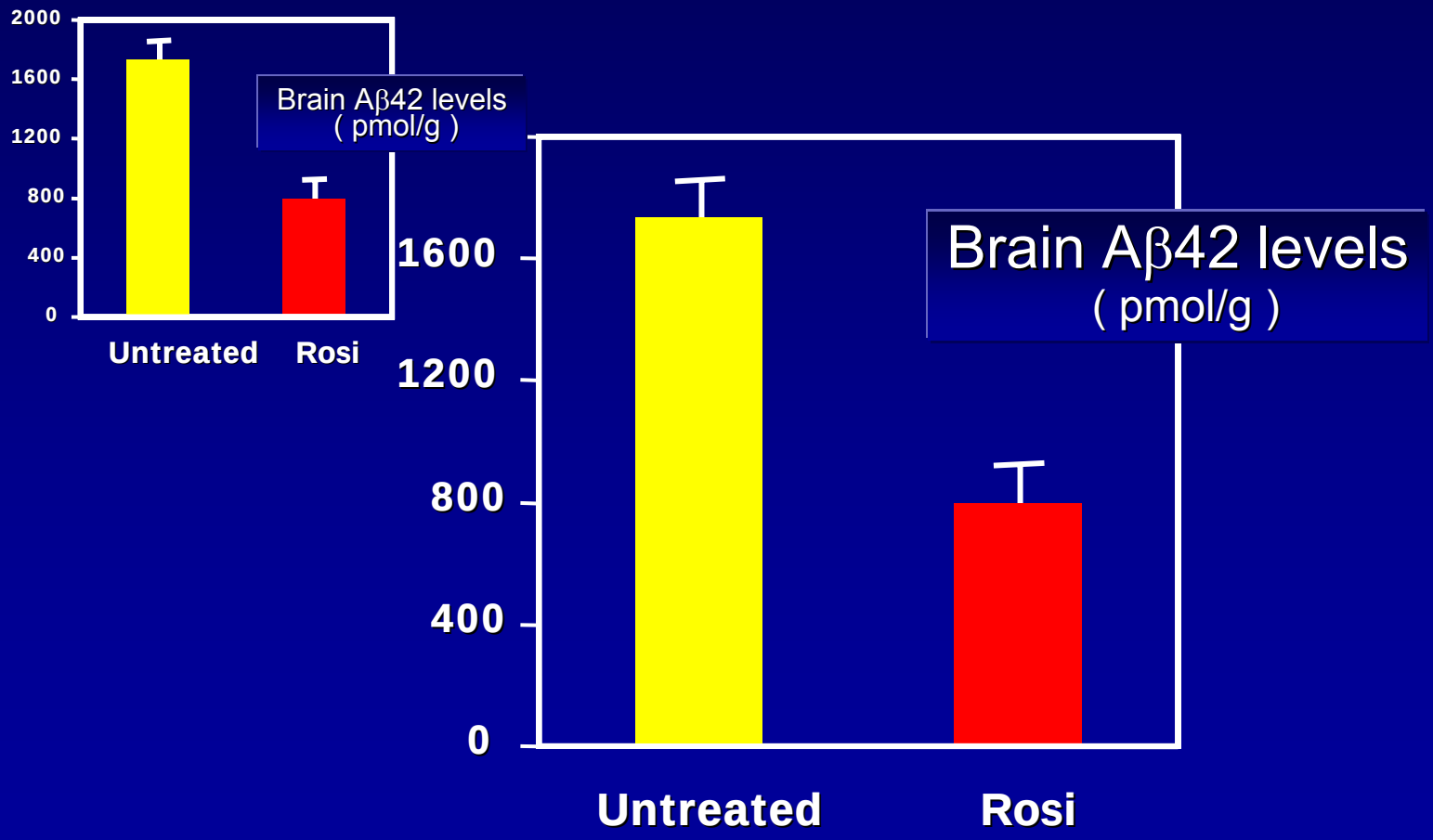


Therapeutic Implications

- Raising plasma insulin invoked age-related increases in CSF Aβ42 & inflammatory markers for normal adults, raised plasma Aβ for AD patients
- Mechanisms through which insulin resistance increases risk of AD with age?
- Treatment of insulin resistance that lowers insulin and improves its effectiveness may be of therapeutic benefit
- PPARγ agonists (TZDs) promising because they increase peripheral insulin sensitivity, reduce peripheral insulin and inflammation

Rosiglitazone Treatment Affects Brain Aβ42, IDE Levels & Memory in AD Mouse Model

9 month old male TG2576 mice treated for 4 mos with 4mg / kg rosiglitazone or placebo



Pedersen et al. Exp Neurol, *in press*

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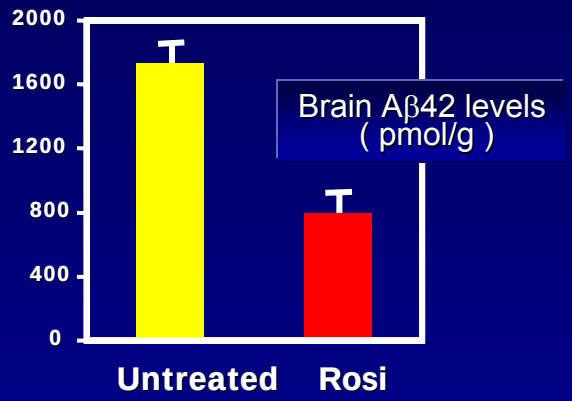
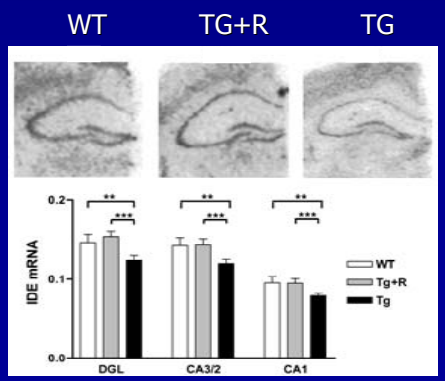
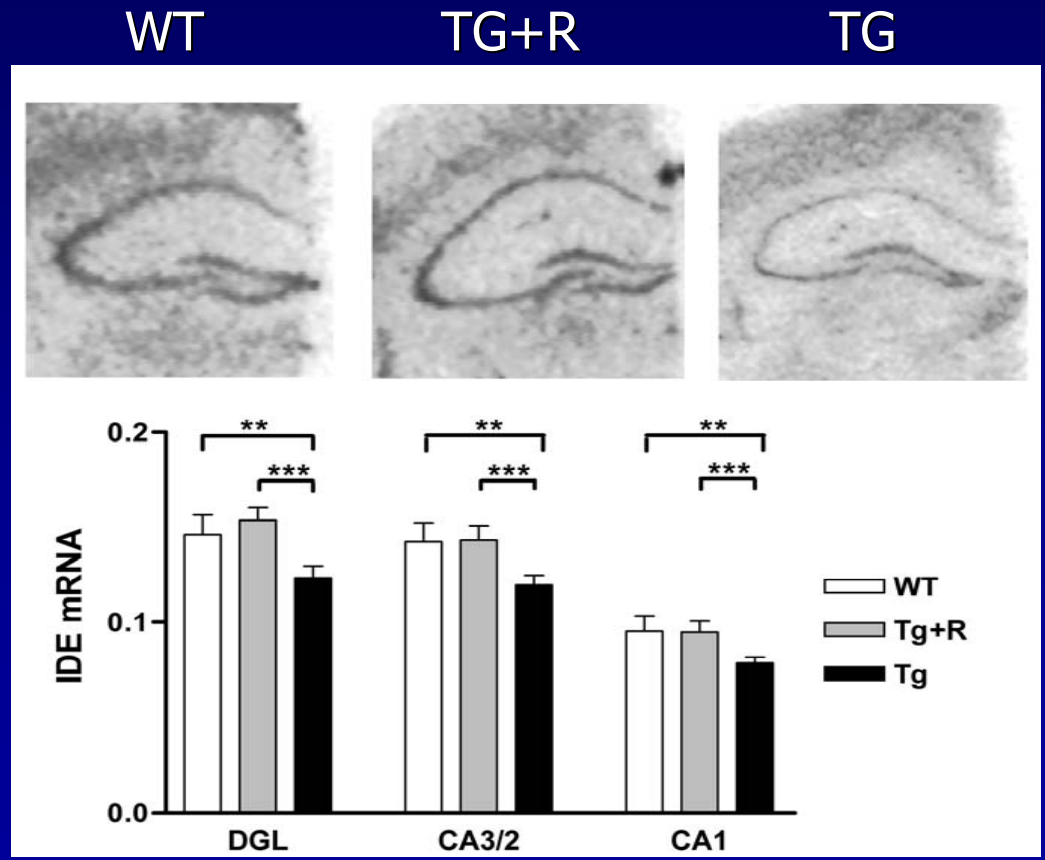




Hippocampal IDE mRNA



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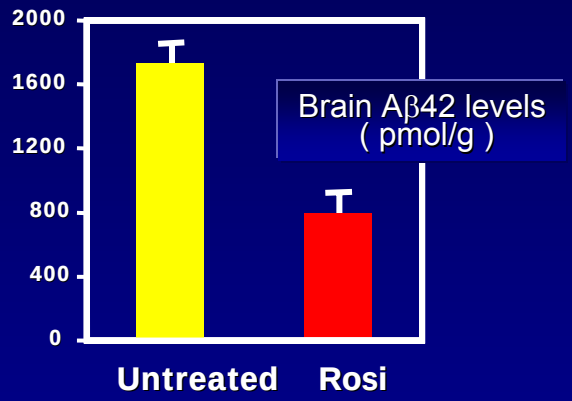

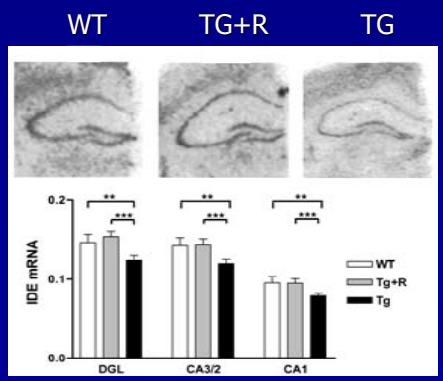

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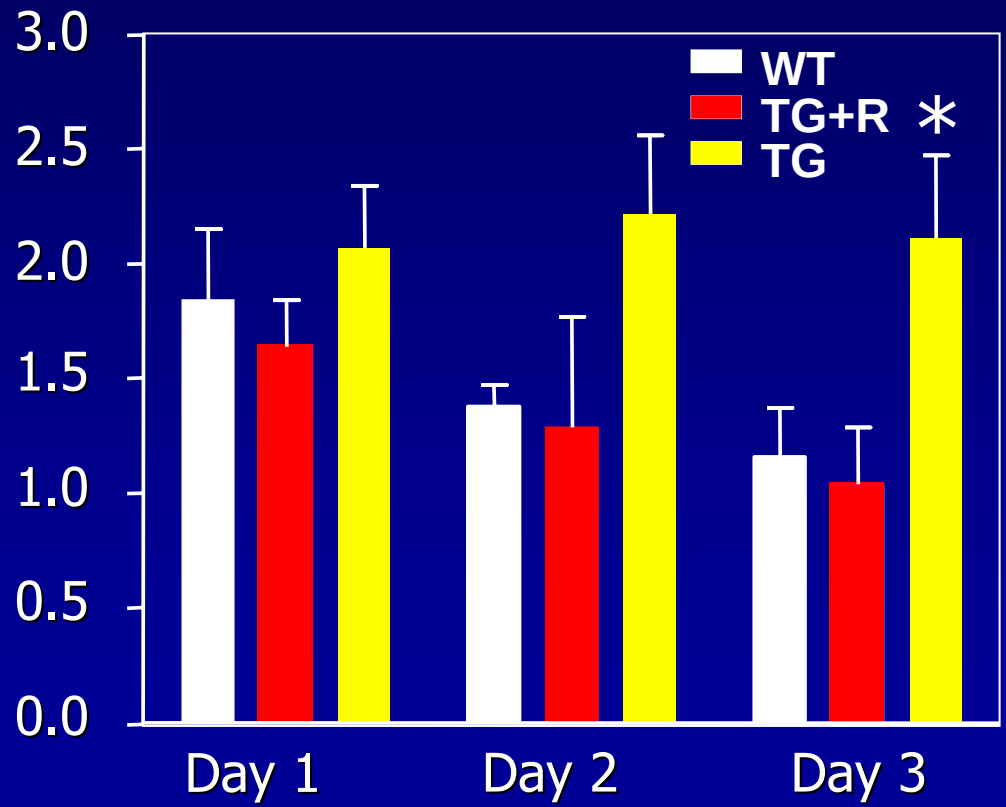


Working Memory Errors

Pedersen et al. Exp Neurol, *in press*

Effects of Rosiglitazone on Cognition in Patients with Early AD or Amnestic MCI

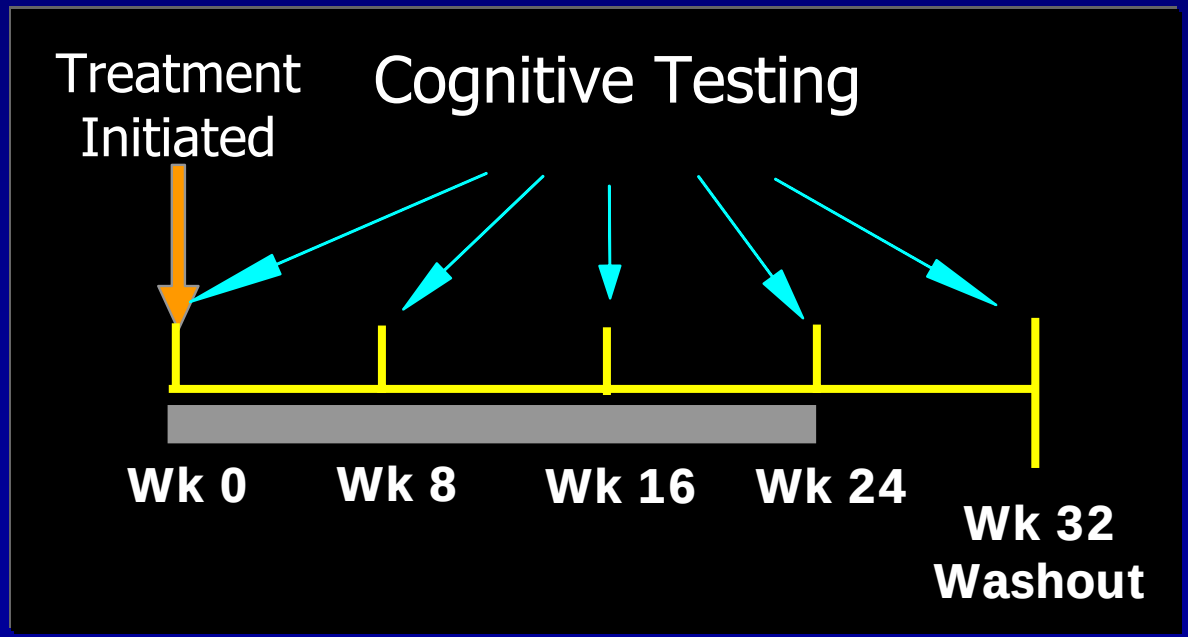
Subjects

- Amnestic MCI or early AD (Petersen et al. 2003 or NINCDS/ADRDA criteria), CDR = 0.5 or 1.0, MMSE > 15
- No diabetes or other relevant medical conditions
- No meds with known CNS effects other than ChEI

Double-blind
Randomized (2:1)

Placebo (n=10)

Rosiglitazone (n=20)



Watson et al. *Am J Geriatr Psychiatry* 2005

Sample Demographics

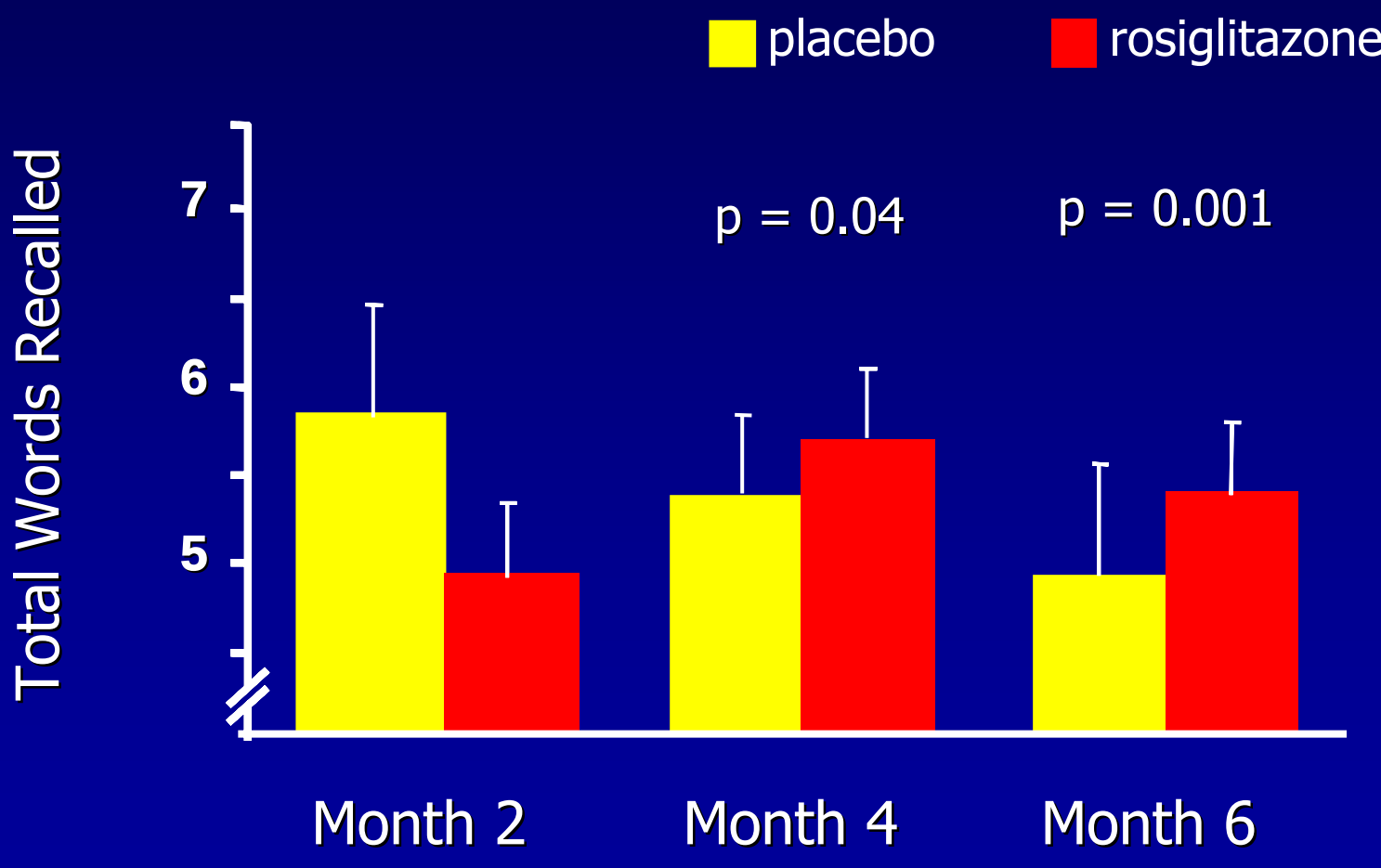
	Rosi (n = 20)	Placebo (n = 10)
Age years	72.8 (6.6)	73.3 (6.0)
AD/MCI	14/6	7/3
Sex (F/M)	6/14	3/7
MMSE	22.7 (4.5)	23.3 (5.4)
BMI	24.2 (2.7)	24.4 (4.2)
ChEI +	25%	20%

Cognitive Battery

- **General Cognition**
  - **Mini Mental State Exam**
- **Memory**
  - **Buschke Reminding Test**
  - **Story Recall**
- **Attention**
  - **Stroop Interference Test**
  - **Trail-Making Test**
- **Language**
  - **Semantic Fluency**
  - **Picture Naming**
  - **Narrative Writing**

Results

Delayed Verbal Memory



Watson GS, et al. *Am J Geriatr Psychiatry* (In press).

Results

- Plasma insulin levels lower after 6 months for rosi-treated group (p=.0026)
- Improvement in memory, selective attention, and verbal fluency related to metabolic treatment response – *indexed by reduced insulin levels*
- No relationship between treatment response and stage of disease

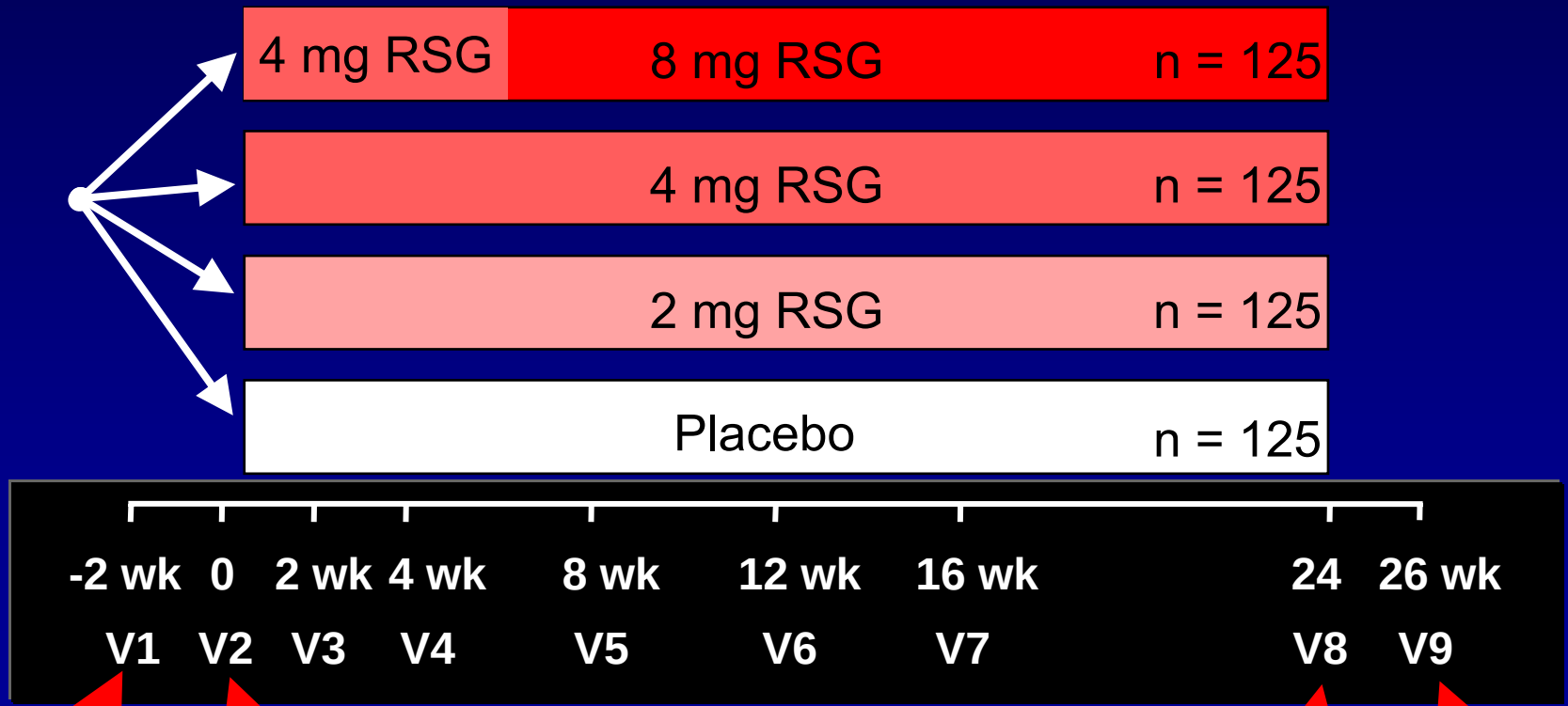
Rosiglitazione XR Study AVA100193

Risner et al., *Pharmacogenomics* J, 2006

- **Population:**
  - **Mild to moderate Alzheimer's Disease (MMSE 16 – 26)**
  - **Treatment naïve, receiving no AD pharmacotherapies**
- **Primary Objectives:**
  - **Cognitive function: *ADAS-cog***
  - **Clinical response: *CIBIC+***
- **Secondary Objectives:**
  - **Other Cognitive/Functional assessments: *NPI, MMSE***
  - **Safety, tolerability: *AEs, hematology, etc***
  - **Insulin sensitivity, glycemic control: *insulin, glucose, etc***
  - **Pharmacogenetics: *interaction by APOE genotype***

GlaxoSmithKline AVA100193

24-week, DB, PBO-controlled, dose-ranging study to investigate rosiglitazone in AD



Risner et al. *Pharmacogenomics J*, 2006

GSK Rosiglitazone Trial : AVA100193
Demographics

	Placebo (N=122)	RSG 2mg (N=127)	RSG 4mg (N=130)	RSG 8mg (N=132)
Gender:				
Female	77 (63%)	71 (56%)	73 (56%)	87 (66%)
Male	45 (37%)	56 (44%)	57 (44%)	45 (34%)
Age:				
Mean (SD)	71.8 (8.2)	70.9 (8.5)	69.7 (9.0)	70.5 (8.5)
Min-Max	50 - 85	50 - 85	50 - 85	51 - 85
BMI:				
Mean (SD)	25.67 (3.8)	25.51 (4.0)	25.88 (3.4)	25.82 (3.9)
MMSE :				
Mean	20.8 (3.44)	21.3 (3.07)	21.6 (2.87)	21.4 (3.20)

Analysis Summary : Change from Baseline in ADAS-Cog at Week 24 (LOCF)

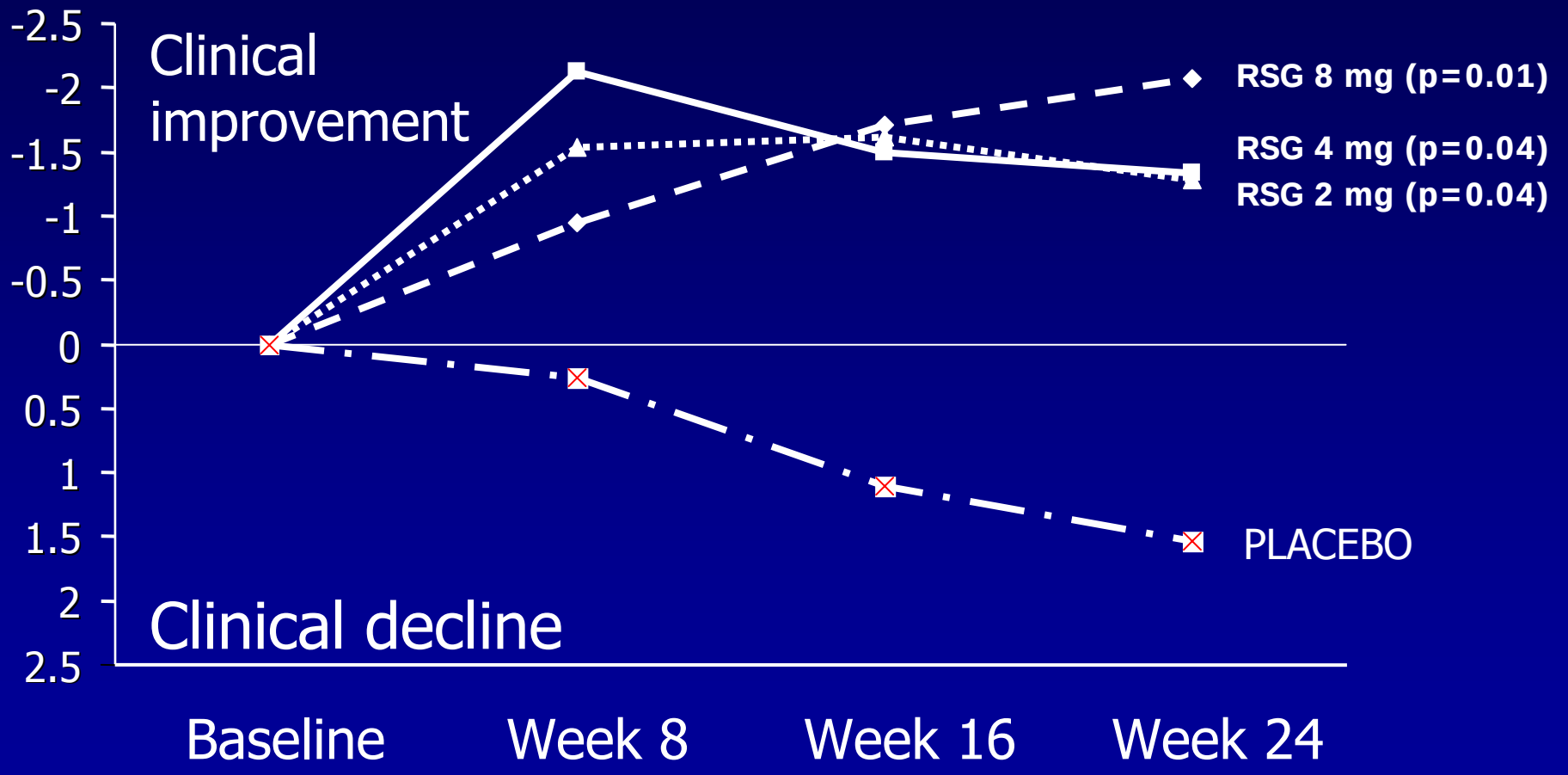
Treatment	N	Least Squares Mean (SE)	Treatment Comparison (RSG vs. Placebo)	
			Difference	***p*-value**
Placebo	122	-0.4 (0.55)		
RSG 2 mg	126	-0.2 (0.54)	0.25	0.74
4 mg	129	-0.9 (0.54)	-0.46	0.52
8 mg	131	-0.7 (0.53)	-0.27	0.71

ADAS-cog assesses various cognitive abilities such as memory, orientation in time and place, etc. Scores range from 0 to 70; higher scores indicate greater dysfunction while negative change indicates improvement

Analysis Summary : Change from Baseline in ADAS-Cog at Week 24 by Treatment & APOE4 Carriage

APOE4 Carriage	Treatment (n)	LS Mean (SE)	*p*-values for Trt Difference*	*p*–value for Interaction
No	Placebo (n =43)	1.10 (0.96)		0.014
	RSG 2 mg (n=49)	-1.35 (0.90)	0.048	
	4 mg (n=45)	-1.21 (0.90)	0.067	
	8 mg (n=42)	-1.84 (0.95)	0.024	
Yes	Placebo (n=35)	-1.10 (1.04)		
	RSG 2 mg (n=36)	2.46 (1.03)	0.012	
	4 mg (n=34)	0.39 (1.05)	0.29	
	8 mg (n=36)	0.39 (1.03)	0.29	

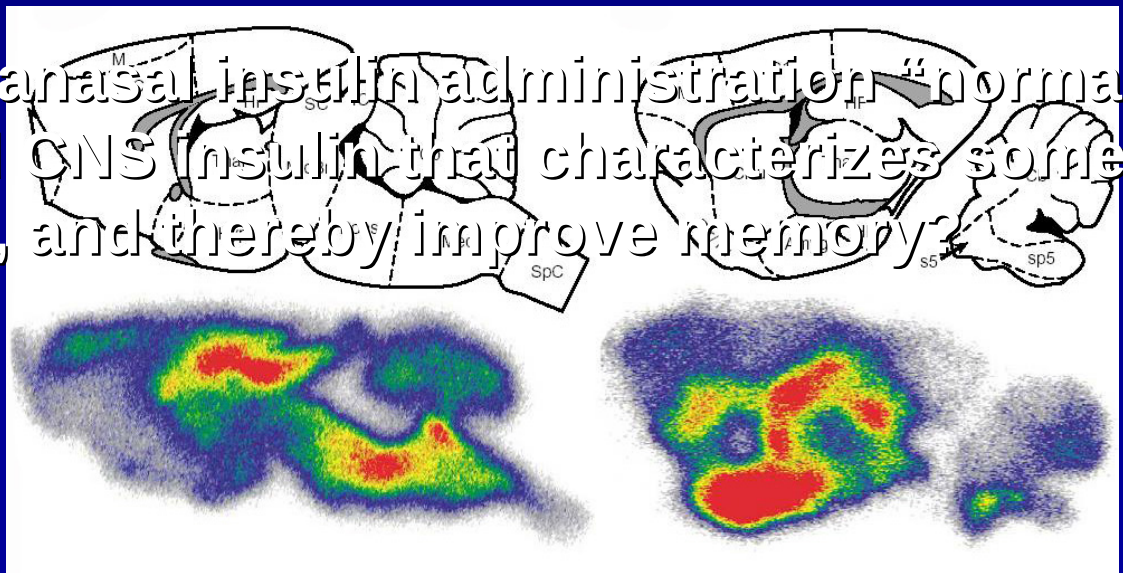
Mean Change from Baseline in ADAS-Cog for APOE4- Subjects Only



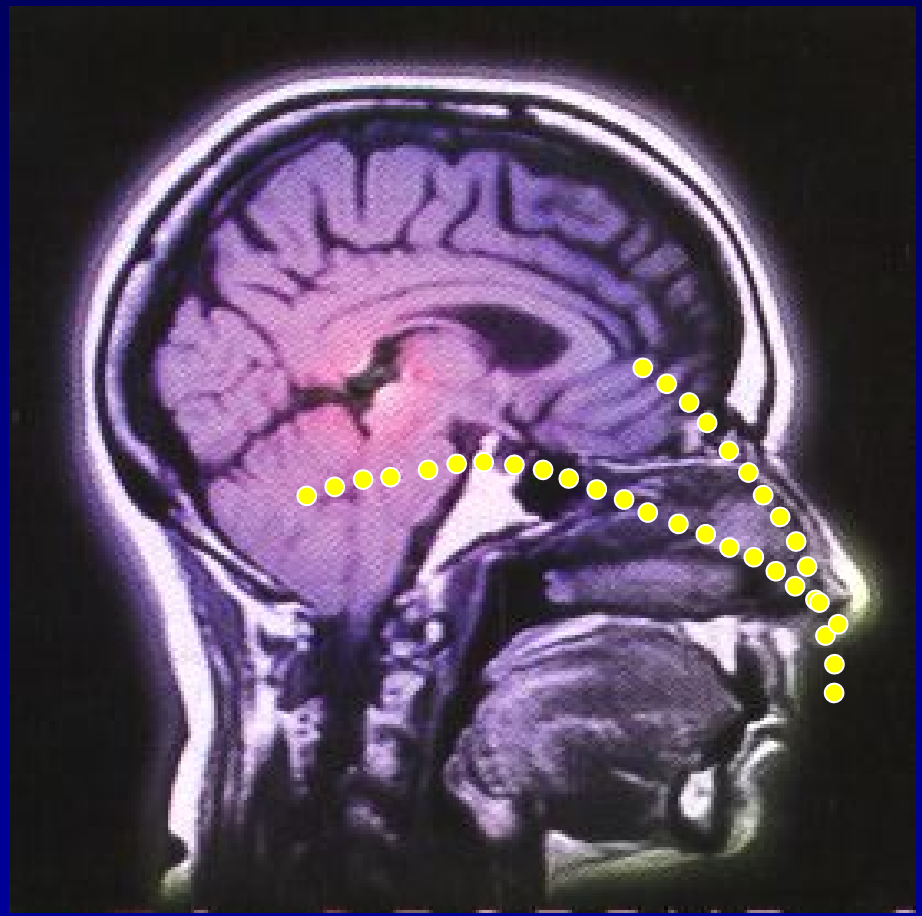
Intranasal Insulin & the CNS

Intranasal insulin administration:

- **Increases CSF insulin and improves memory within 30-min in young, healthy adults without changing plasma glucose or insulin (Born et al. 02; Benedict et al. 04)**
- **Insulin-like peptide signal measurable in rat hippocampus, amygdala, frontal cortex 30 min after intranasal administration (Thorne et al. 04)**
- **Can intranasal insulin administration "normalize" reduced CNS insulin that characterizes some patients with AD, and thereby improve memory?**



Intranasal Pathways to the Brain in Humans



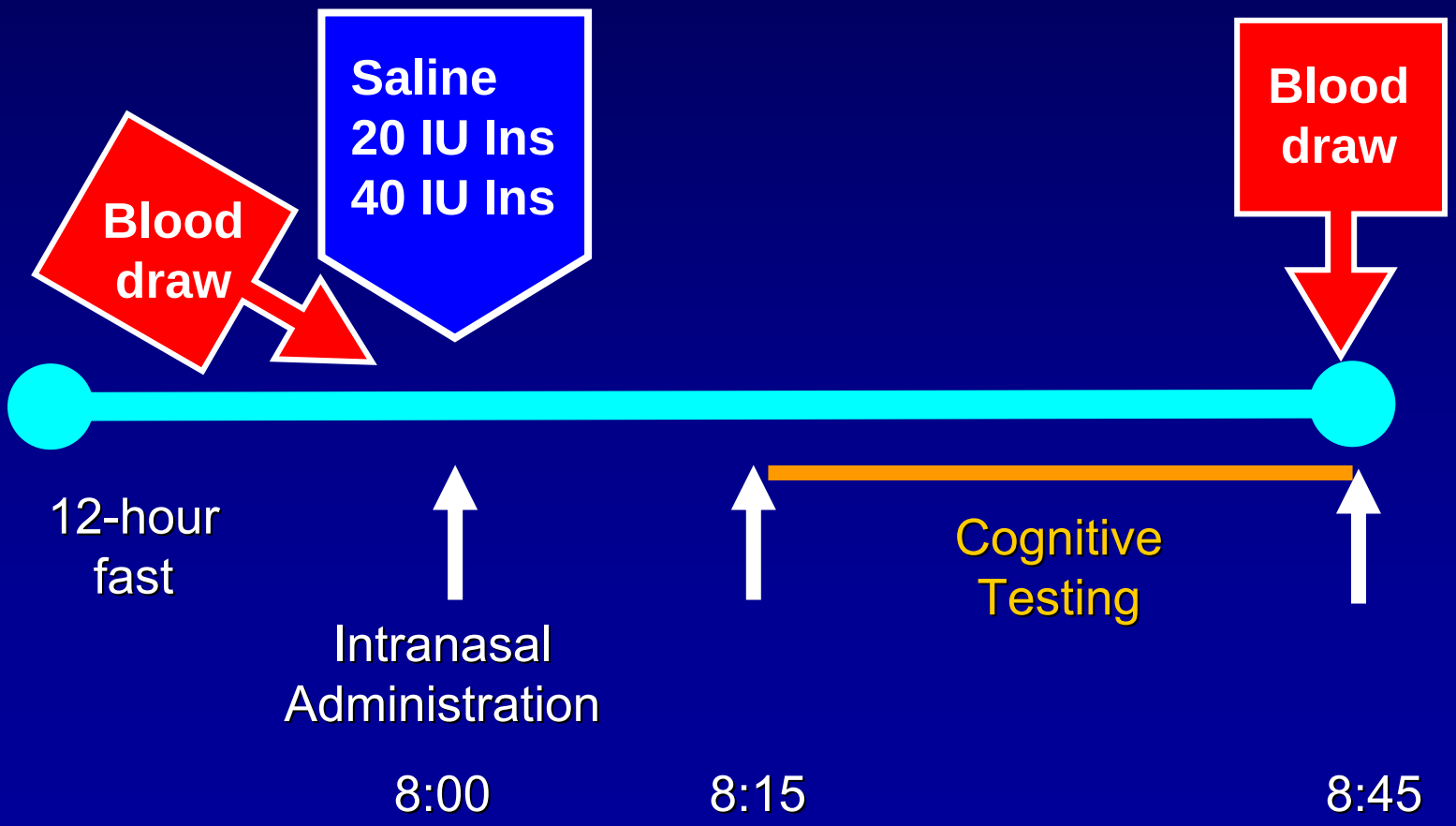
- Bulk flow along rostral (olfactory) or caudal (trigeminal) perivascular channels; agents reach brain in minutes

  (Thorne et al. 01)

- Axonal transport through olfactory neurons, which require hours to reach brain

Study 1 Methods

Procedure



Study 1 Methods

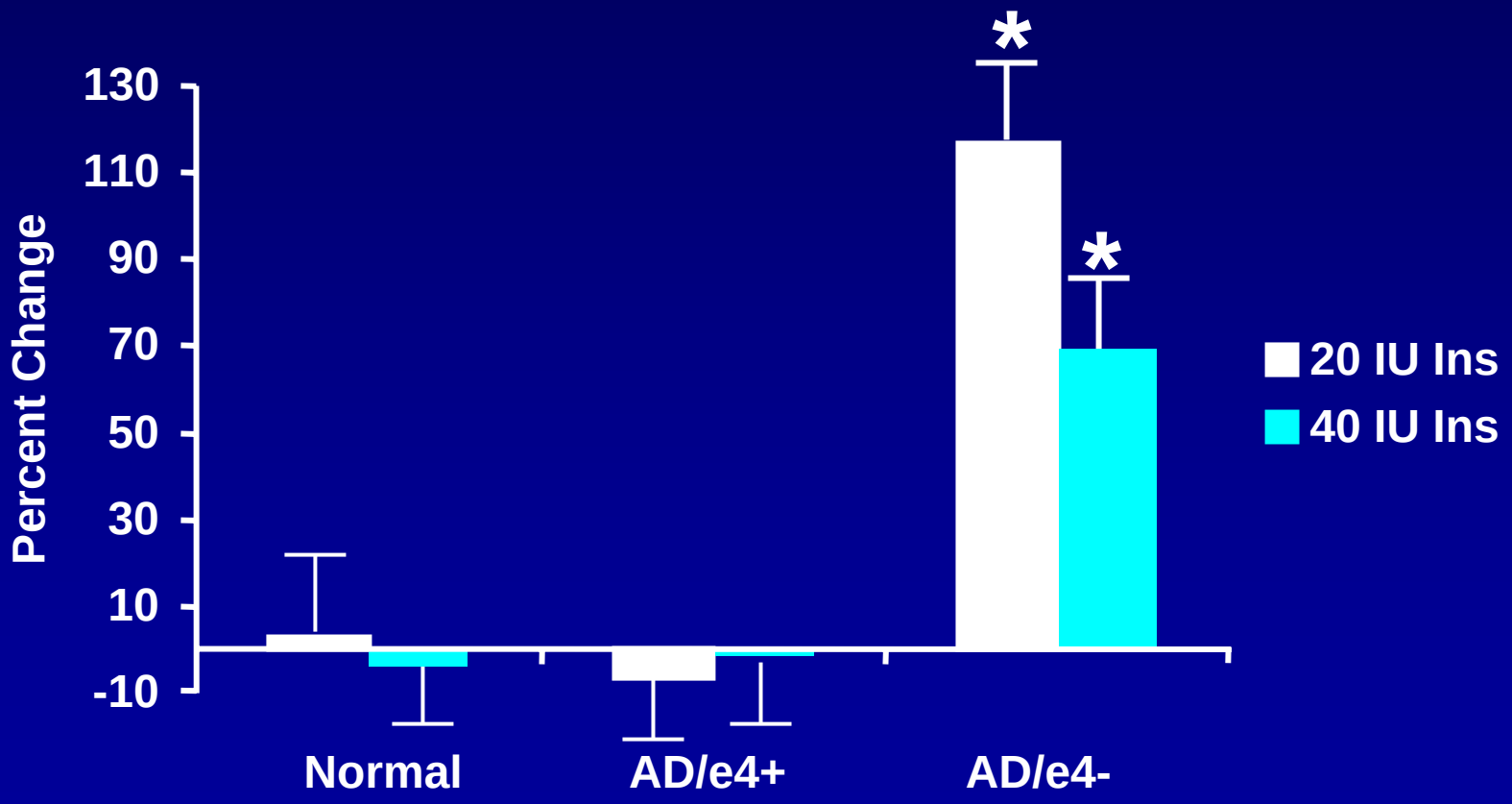
Subjects

Mean (sd)	Normal Controls	AD ε4-	AD ε4+
N	35	14	12
Age (yrs)	75 (6)	77 (6)	77 (5)
Education	15 (2)	14 (2)	15 (2)
BMI (kg/m^2)	26 (3)	25 (3)	25 (3)
DRS (max=144)	140 (4)	127 (10)	125 (11)

Study 1

Results

Total Story Recall



Reger et al. Neurobio Aging 2006

Study 2 Methods

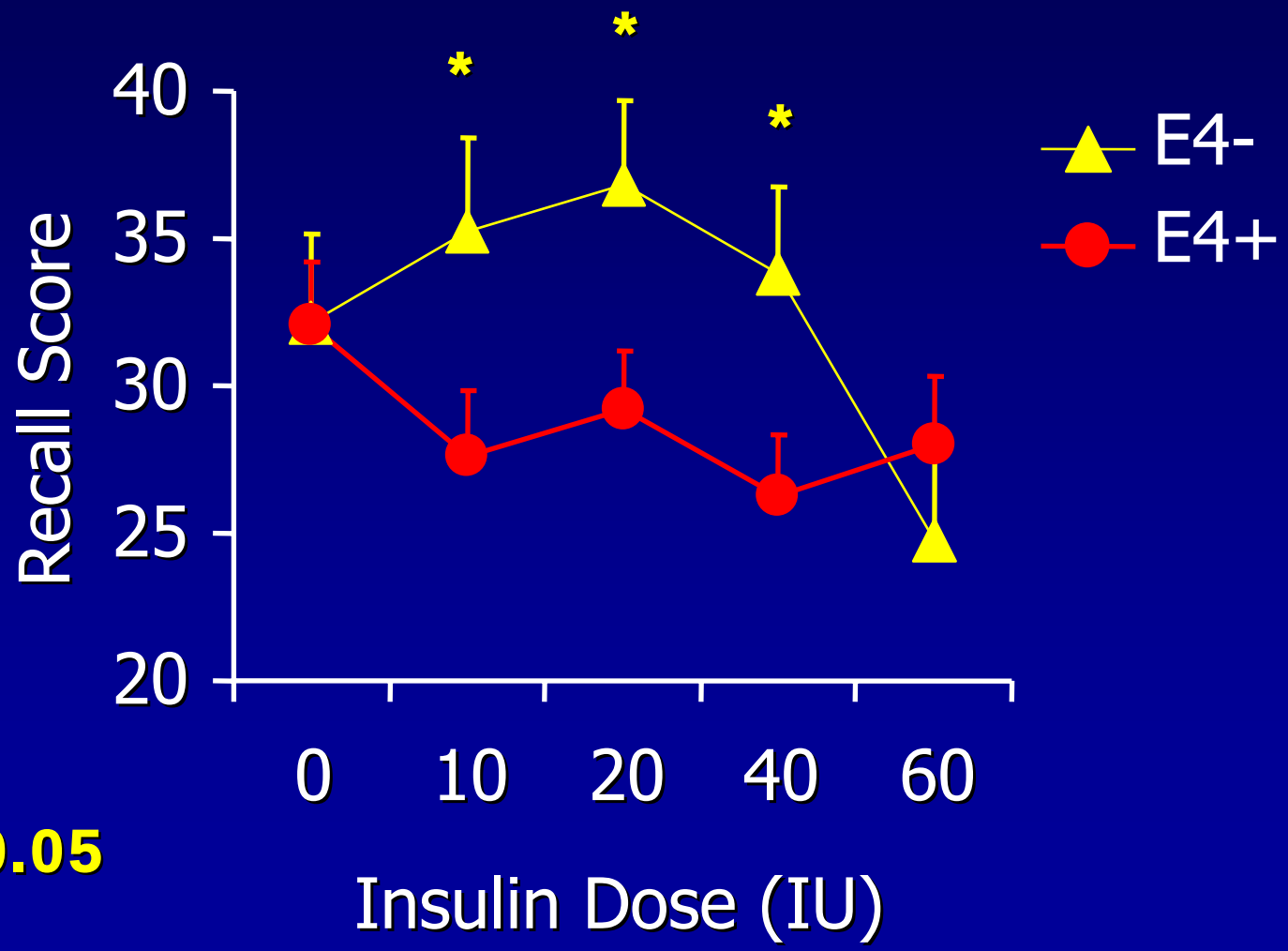
Subjects

Mean (sd)	AD ε4-	AD ε4+
N	11	23
Age (yrs)	76 (4)	77 (8)
Education	14 (3)	15 (3)
BMI (kg/m^2)	26 (3)	26 (5)
DRS (max=144)	131 (9)	130 (13)

Study 2

Results

Total Story Recall



*** p<0.05**

Summary

- Insulin has numerous actions in CNS that affect cognition
- Hyperinsulinemia / insulin resistance increases inflammation and CSF Aβ42
- These conditions may be potent AD risk factors, particularly for patients *without* APOE ε4-
- Treatment with PPARγ agonist rosiglitazone & intranasal insulin enhance cognition in AD / amnestic MCI – may represent novel therapeutic strategies for this subgroup of patients

Collaborators

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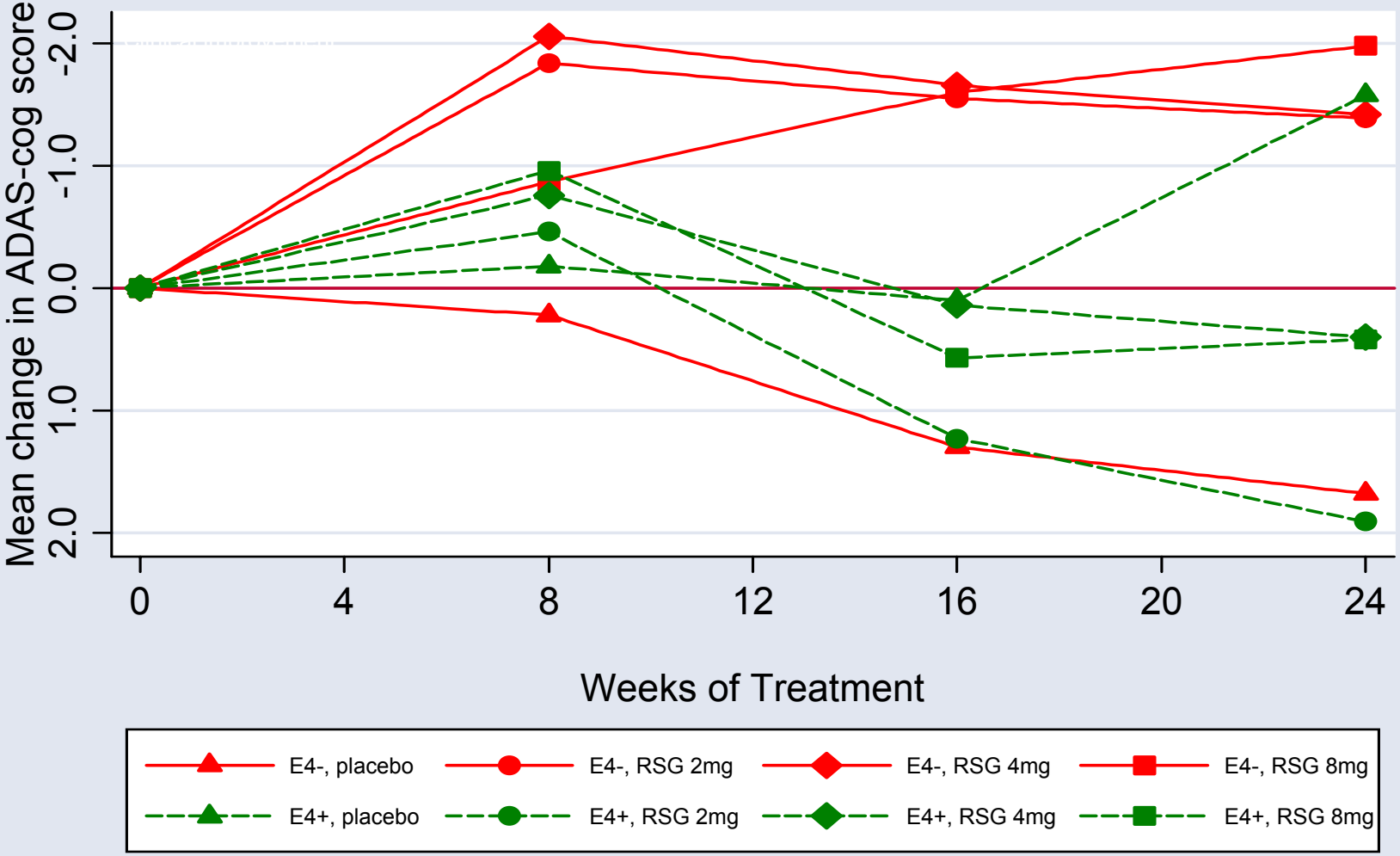
Amy Morgan
Mark Reger, PhD
Stennis Watson, PhD
Magdalena Wojtowicz

Exclusionary Criteria

- Significant neurological disease other than AD
- Use of antidepressants, antipsychotics, anticonvulsants, anticoagulants, anxiolytics or sedatives
- Major psychiatric disorders
- Severe head trauma with LOC >30 min or with permanent sequelae
- Uncontrolled chronic pain
- Radiation treatment (current or recent)
- CVA
- CHF
- COPD
- Vision loss
- Diabetes (diagnosed)
- Alcohol and drug abuse/dependence
- Liver disease
- Severe medical illness (e.g., uncontrolled HTN, cancer not in remission > 1 year, thyroid disease, cardiac arrhythmia, renal and hepatic disease)

Model-adjusted Mean Change from Baseline in ADAS-cog by APOE4 status



Safety Data

- Safety monitoring (labs, physical exam) at weeks 2 and 4, then monthly
- No changes in fasting glucose, lipids, LFTs, renal indices
- Two SAEs: Myocardial infarction (1 placebo) and lacunar infarction (1 rosi)
- Other AEs: mild anemia (1 placebo, 3 rosi), mild edema (1 rosi)

AVA100193: Key Safety Results, ITT Population

Summary of AEs/SAEs	Placebo (N = 124)	RSG 2mg (N = 128)	RSG 4mg (N = 131)	RSG 8mg (N = 135)
Any Tx emergent AE	44 (35%)	36 (28%)	41 (31%)	46 (34%)
Any SAE	7 (6%)	6 (5%)	3 (2%)	9 (7%)

AEs of Special Interest

	Placebo (N = 124)	RSG 2mg (N = 128)	RSG 4mg (N = 131)	RSG 8mg (N = 135)
Oedema	0	3 (2%)	1 (<1%)	3 (2%)
Oedema peripheral	0	0	4 (3%)	3 (2%)
Eyelid oedema	0	1 (<1%)	0	1 (<1%)
Periorbital oedema	1 (<1%)	0	0	0
Anaemia	0	1 (<1%)	0	2 (1%)
Cardiac failure	1 (<1%)	0	0	1 (<1%)
Cardiac failure (acute)	0	0	1 (<1%)	0
Alanine aminotransferase ↑	0	0	0	1 (<1%)
Aspartate aminotransferase ↑	0	0	0	1 (<1%)

No new safety concerns identified in AVA100193 compared with the well established safety profile of rosiglitazone