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 $\beta$-amyloid
- Therapeutic applications: Effects of treating insulin resistance and normalizing 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
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)

Insulin/dextrose or saline infusion

IV

Plasma glucose measured every 5-10 min

90 min, 105 min

Cognitive testing

LP for CSF collection
Effects of Insulin on CSF Aβ42 Levels in Normal Older Adults: Results

Insulin-induced change in Aβ42 is correlated with age

r = .64, p < .008

< 70 yrs

≥ 70 yrs

r = .85
p < .008

Results

Cytokines

CSF IL-1\(\alpha\) (pg / ml)

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF IL-6 (pg / ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>

CSF IL-1\(\beta\) (pg / ml)

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF TNF(\alpha) (pg / ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Insulin</td>
<td>3.5</td>
<td>3</td>
</tr>
</tbody>
</table>

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

CSF F2-Isoprostane levels increase in response to insulin

<table>
<thead>
<tr>
<th>F2-IsoP (pg / ml)</th>
<th>Saline</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < .01
Results

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

- **ALL**: $r = .15, p = ns$
- **OLD**: $r = .87, p = .005$
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

% change in plasma Aβ42

* p=0.009

Reger et al. *in press*
Model of Peripheral Insulin Resistance & Hyperinsulinemia Effects on $A_\beta$ Regulation

- **CENTRAL NERVOUS SYSTEM**
  - LOW INSULIN LOW IDE
  - $A_\beta$

- **CNS MICROVASCULATURE AND BLOOD-BRAIN BARRIER**
  - HIGH INSULIN & INSULIN RESISTANCE
  - ADIPOCYTES
  - FFA & TNF$\alpha$

- **PERIPHERY**
  - IDE
  - $A_\beta$
  - MUSCLE
  - LIVER
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
Rosiglitazone Treatment Affects Brain Aβ42, IDE Levels & Memory in AD Mouse Model

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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)

Treatment Initiated
Cognitive Testing

Watson et al. Am J Geriatr Psychiatry 2005
## Sample Demographics

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

## 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


Total Words Recalled

Month 2  Month 4  Month 6

placebo  rosiglitazone

$p = 0.04$  $p = 0.001$
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
Rosiglitazone XR Study AVA100193

Risner et al., *Pharmacogenomics*, 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

- 4 mg RSG
- 8 mg RSG
- 4 mg RSG
- 2 mg RSG
- Placebo

n = 125

-2 wk 0 2 wk 4 wk 8 wk 12 wk 16 wk 24 26 wk
V1 V2 V3 V4 V5 V6 V7 V8 V9

Screening Randomization End of Treatment
Follow-up

Risner et al. *Pharmacogenomics J*, 2006
### GSK Rosiglitazone Trial: AVA100193

#### Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Placebo (N=122)</th>
<th>RSG 2mg (N=127)</th>
<th>RSG 4mg (N=130)</th>
<th>RSG 8mg (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>77 (63%)</td>
<td>71 (56%)</td>
<td>73 (56%)</td>
<td>87 (66%)</td>
</tr>
<tr>
<td>Male</td>
<td>45 (37%)</td>
<td>56 (44%)</td>
<td>57 (44%)</td>
<td>45 (34%)</td>
</tr>
<tr>
<td><strong>Age:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>71.8 (8.2)</td>
<td>70.9 (8.5)</td>
<td>69.7 (9.0)</td>
<td>70.5 (8.5)</td>
</tr>
<tr>
<td>Min-Max</td>
<td>50 - 85</td>
<td>50 - 85</td>
<td>50 - 85</td>
<td>51 - 85</td>
</tr>
<tr>
<td><strong>BMI:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>25.67 (3.8)</td>
<td>25.51 (4.0)</td>
<td>25.88 (3.4)</td>
<td>25.82 (3.9)</td>
</tr>
<tr>
<td><strong>MMSE:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>20.8 (3.44)</td>
<td>21.3 (3.07)</td>
<td>21.6 (2.87)</td>
<td>21.4 (3.20)</td>
</tr>
</tbody>
</table>
## Analysis Summary: Change from Baseline in ADAS-Cog at Week 24 (LOCF)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Least Squares Mean (SE)</th>
<th>Treatment Comparison (RSG vs. Placebo)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference</td>
</tr>
<tr>
<td>Placebo</td>
<td>122</td>
<td>-0.4 (0.55)</td>
<td></td>
</tr>
<tr>
<td>RSG 2 mg</td>
<td>126</td>
<td>-0.2 (0.54)</td>
<td>0.25</td>
</tr>
<tr>
<td>4 mg</td>
<td>129</td>
<td>-0.9 (0.54)</td>
<td>-0.46</td>
</tr>
<tr>
<td>8 mg</td>
<td>131</td>
<td>-0.7 (0.53)</td>
<td>-0.27</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>APOE4 Carriage</th>
<th>Treatment (n)</th>
<th>LS Mean (SE)</th>
<th>p-values for Trt Difference*</th>
<th>p-value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Placebo (n =43)</td>
<td>1.10 (0.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSG 2 mg (n=49)</td>
<td>-1.35 (0.90)</td>
<td>0.048</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mg (n=45)</td>
<td>-1.21 (0.90)</td>
<td>0.067</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 mg (n=42)</td>
<td>-1.84 (0.95)</td>
<td>0.024</td>
<td></td>
<td>0.014</td>
</tr>
<tr>
<td>Yes</td>
<td>Placebo (n=35)</td>
<td>-1.10 (1.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSG 2 mg (n=36)</td>
<td>2.46 (1.03)</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mg (n=34)</td>
<td>0.39 (1.05)</td>
<td>0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 mg (n=36)</td>
<td>0.39 (1.03)</td>
<td>0.29</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mean Change from Baseline in ADAS-Cog for APOE4- Subjects Only

Clinical improvement

Clinical decline

Baseline  Week 8  Week 16  Week 24

RSG 8 mg (p=0.01)
RSG 4 mg (p=0.04)
RSG 2 mg (p=0.04)

PLACEBO
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**

- **Blood draw**
  - Saline 20 IU Ins 40 IU Ins
  - Intranasal Administration
  - 12-hour fast
  - Cognitive Testing
  - Blood draw

- 8:00
- 8:15
- 8:45
### Study 1

#### Methods

#### Subjects

<table>
<thead>
<tr>
<th>Mean (sd)</th>
<th>Normal Controls</th>
<th>( \varepsilon 4^- )</th>
<th>( \varepsilon 4^+ )</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>35</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>75 (6)</td>
<td>77 (6)</td>
<td>77 (5)</td>
</tr>
<tr>
<td>Education</td>
<td>15 (2)</td>
<td>14 (2)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>26 (3)</td>
<td>25 (3)</td>
<td>25 (3)</td>
</tr>
<tr>
<td>DRS (max=144)</td>
<td>140 (4)</td>
<td>127 (10)</td>
<td>125 (11)</td>
</tr>
</tbody>
</table>
## Study 2

### Methods

#### Subjects

<table>
<thead>
<tr>
<th>Mean (sd)</th>
<th>AD</th>
<th>ɛ4-</th>
<th>ɛ4+</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td></td>
<td>76 (4)</td>
<td>77 (8)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td>14 (3)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td></td>
<td>26 (3)</td>
<td>26 (5)</td>
</tr>
<tr>
<td>DRS (max=144)</td>
<td></td>
<td>131 (9)</td>
<td>130 (13)</td>
</tr>
</tbody>
</table>
Study 2

Results

Total Story Recall

Recall Score vs. Insulin Dose (IU)

* p<0.05

**E4-**

**E4+**
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

<table>
<thead>
<tr>
<th>Sanjay Asthana, MD</th>
<th>Steven Kahn, MB, ChB</th>
</tr>
</thead>
<tbody>
<tr>
<td>John Breitner, MD, MPH</td>
<td>James Leverenz, MD</td>
</tr>
<tr>
<td>David Cook, PhD</td>
<td>Thomas Montine, MD, PhD</td>
</tr>
<tr>
<td>Mark Fishel, MD</td>
<td>Ward Pedersen, PhD</td>
</tr>
<tr>
<td>Pattie Green, PhD</td>
<td>Elaine Peskind, MD</td>
</tr>
<tr>
<td>William Frey, II, PhD</td>
<td>Stephen Plymate, MD</td>
</tr>
<tr>
<td></td>
<td>Murray Raskind, MD</td>
</tr>
</tbody>
</table>

This work was funded by the Department of Veterans Affairs, NIA R01 AG10880, ISOA, and GlaxoSmithKline.
Insulin and Neurodegenerative Disease Research Team

Pamela Asberry, RN
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Karen Enstrom, RN
Mark Fishel, MD
Laura Fisher
Laura Frank, PhD
Maggie Gillet
Karen Hyde, RN
Jamie Iliff
Jake Kulstad
Marcos Marques, MD
Pamela McMillan, PhD
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

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

### AEs of Special Interest

<table>
<thead>
<tr>
<th>AEs of Special Interest</th>
<th>Placebo (N = 124)</th>
<th>RSG 2mg (N = 128)</th>
<th>RSG 4mg (N = 131)</th>
<th>RSG 8mg (N = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oedema</td>
<td>0</td>
<td>3 (2%)</td>
<td>1 (&lt;1%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>0</td>
<td>0</td>
<td>4 (3%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Eyelid oedema</td>
<td>0</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Periorbital oedema</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Cardiac failure (acute)</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferase↑</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Aspartate aminotransferase↑</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

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