Debate:
Insulin &
Alzheimer’s Disease

Mary ET Boyle, Ph. D.
Department of Cognitive Science
UCSD
Insulin and cognition

- **Insulin resistance induces:**
  - Chronic hyperinsulinemia
  - Reduces insulin activity
  - Reduces brain insulin levels
  - Insulin resistance syndrome, diabetes type 2
  - Associated with age-related memory impairment

Insulin and Memory

- What is the role of insulin in memory?
- How does insulin dysregulation contribute to memory impairment?
- Is the memory impairment associated with Alzheimer disease?
- Is the memory impairment age related?
conditions of insulin dysregulation:

- impaired glucose tolerance & diabetes
- insulin resistance – direct and indirect pathways
- co-morbid: cardiovascular disease and hypertension
- what is the effect on brain function?
insulin facilitates memory

under normal physiological conditions

optimal doses & sufficient glucose availability

direct administration of insulin in the brain

intranasal insulin administration modulates memory in AD patients.

http://www.adcs.org/studies/SNIFF.aspx
A small study published Tuesday in the Archives of Neurology found preliminary evidence that spraying critical insulin deep into the nose could help delay the onset of Alzheimer's disease. Ray Suarez speaks with University of Washington School of Medicine professor Suzanne Craft, who led the study.
Dr. Suzanne Craft

Glucose use in placebo vs. low dose insulin

http://www.pbs.org/newshour/bb/health-july-dec11-alzheimers_09-12/
intranasal administration

administration of insulin in the brain does not alter the basal brain glucose uptake. It does modulate glucose utilization in selective CNS circuits.

- insulin-like peptides follow perivascular channels
- location of insulin receptors in the brain is important
- no effect on peripheral glucose levels
- hippocampus, entorhinal cortex, frontal lobe
intranasal administration

- affects circuits important for cognitive function
- affects LTP
- classic neurotransmitters are affected
- hippocampus, entorhinal cortex, frontal lobe

affects levels of acetylcholine (Ach), norepinephrine (NE) and dopamine (DA)
Insulin resistance syndrome

- Persistent extreme elevations of insulin
- Reduced insulin activity in the periphery
- Can be induced by defects at the levels of the insulin receptor
- Or post-receptor abnormalities in the insulin signaling pathway

IR can become hyperinsulinemia.
increased plasma levels of insulin; gene ablation; glucocorticoid administration; excess insulin production or reduced clearance. negative feedback mechanism? down-regulation of insulin signaling pathway.
double whammy for older adults:

- chronic hyperinsulinemia
- diminished positive effects of insulin in the brain
- reduced insulin transport into brain
- brain insulin deficiency

in the periphery:
- increased free fatty acids
- inflammatory cytokines
hyperinsulinemic-euglycemic clamp

- Effects of hyperinsulinemia acutely
- Insulin is infused intravenously at a continuous rate to reach a predetermined level
- Dextrose is administered as needed at a variable rate to maintain euglycemia
- Patients with AD using hyperinsulinemic-euglycemic clamp
- Low doses of insulin, memory is facilitated for normal older adults
- AD likely to have insulin resistance syndrome require higher insulin doses to show memory facilitation
Insulin increases CSF Aβ42 levels in normal older adults

G.S. Watson, PhD; E.R. Peskind, MD; S. Aethana, MD; K. Purganan, BS; C. Wait, BS; D. Chapman, BSN; M.W. Schwartz, MD; S. Plymate, MD; and S. Craft, PhD

Abstract—Background: Abnormal insulin metabolism may contribute to the clinical symptoms and pathophysiology of AD. In vitro studies show that insulin enhances the release of B-amyloid protein (Aβ) or inhibits its degradation, either of which might increase amyloid burden. Method: On separate mornings, 16 healthy older adults (10 women, 6 men; mean age 68.7 years, SD 8.6 years) each underwent two infusions consisting of either saline (placebo) or insulin (1.0 mU/kg^-1 min^-1) plus dextrose to maintain euglycemia. After 120 minutes of infusion, blood, CSF, and cognitive measures were acquired. Results: As expected, insulin infusion produced an increase in CSF insulin concentration. Insulin infusion also led to an increase in CSF Aβ42 levels, most notably in older subjects. As has been observed previously, insulin infusion facilitated declarative memory, but such facilitation was attenuated in the subjects with the greatest increase in CSF Aβ42 levels. Conclusion: These findings are consistent with recent in vitro studies of insulin effects on Aβ and support the notion that insulin may modulate Aβ42 levels acutely in humans.


Discussion. CSF Aβ42 levels increased with insulin administration, an effect that was more pronounced in older adults. Increased CSF insulin following peripheral infusion reflects increased brain insulin concentrations. Our results are therefore consistent with the notion that elevated brain insulin levels contribute to increased concentrations of CSF Aβ42. Although we cannot determine the precise mechanism for this effect, previous in vitro studies suggest several possibilities. Insulin may promote release of Aβ42 from intracellular compartments into CSF. Insulin infusion may also impede degradation of Aβ42, as suggested by findings that insulin inhibits IDE-mediated Aβ clearance.9

In the current study, the association of increased CSF Aβ42 with increased CSF insulin concentration after insulin infusion was strengthened markedly with age. This pattern may reflect a greater vulnerability of older adults to the effects of insulin on Aβ42 degradation or release. There was no relationship between age and CSF Aβ42 levels with saline infusion, however. Thus, to the extent that CSF and brain Aβ42 levels are correlated, the effects of insulin do not seem to be due to the increased availability of Aβ42. Furthermore, recent studies of large num-

1902 NEUROLOGY 60 June (2 of 2) 2003

insulin modulates B-amyloid peptide
Elevated insulin in the brain is not good.

Increased plasma levels of insulin increased levels of amyloid-β in CSF.

A, Percent CSF A[beta]42 increase after insulin infusion relative to saline infusion was age-dependent, with older adults showing larger increases ($P<0.01$).

B, Insulin-induced A[beta]42 changes were negatively correlated with insulin-induced memory facilitation for older (age>70) adults ($r=-0.95$, $P<0.01$).

Peripheral hyperinsulinemia increases inflammation response raising insulin increased CSF levels of proinflammatory cytokines interleukin (IL)-1[beta], IL-6, tumor necrosis factor-[alpha], F2-IsoProstane
is insulin resistance really associated with AD?

- new evidence?
- glucose intolerance is not associated with AD?
- insulin resistance does not appear to be associated with βAmyloid accumulation
- Baltimore Longitudinal Study of Aging
Conclusions and Relevance  In this prospective cohort with multiple assessments of glucose intolerance and insulin resistance, measures of glucose and insulin homeostasis are not associated with AD pathology and likely play little role in AD pathogenesis. Long-term therapeutic trials are important to elucidate this issue.

the study:

what is the relationship between glucose intolerance and Aβ burden?


glucose tolerance tests while alive and then autopsy and second group with glucose tolerance test and then imaged PIB (Pittsburgh Compound B) PET scans
the question: is the cognitive impairment seen in T2D mediated by AD pathology? Could it be mediated by something else, eg. vascular disease?

<table>
<thead>
<tr>
<th>Autopsy Cohort, Mean (SD)</th>
<th>No Medication to Lower Glucose Level (n = 181)</th>
<th>Any Medication to Lower Glucose Level (n = 30)</th>
<th>Any Insulin Use (n = 9)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of use</td>
<td>NA</td>
<td>14.3 (8.2)</td>
<td>7.4 (3.4)</td>
<td>NA</td>
</tr>
<tr>
<td>Braak score</td>
<td>3.5 (1.2)</td>
<td>3.3 (1.5)</td>
<td>3.3 (1.0)</td>
<td>.53</td>
</tr>
<tr>
<td>Peak CERAD score</td>
<td>1.6 (1.2)</td>
<td>1.6 (1.0)</td>
<td>1.7 (0.8)</td>
<td>.81</td>
</tr>
<tr>
<td>Mean CERAD score</td>
<td>1.3 (1.0)</td>
<td>1.4 (1.0)</td>
<td>1.4 (0.7)</td>
<td>.76</td>
</tr>
<tr>
<td>Composite AD pathology score</td>
<td>3.7 (1.3)</td>
<td>3.7 (1.2)</td>
<td>3.6 (0.6)</td>
<td>.93</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; CERAD, Consortium to Establish a Registry for Alzheimer’s Disease; NA, not applicable.