Is Alzheimer's Disease Type 3 Diabetes?

Vasileios Papaliagkas, Kazakos K, Gkioka M, Mousiolis A, Tsolaki M

Neurologist, MD/PhD
Laboratory of Clinical Neurophysiology, Aristotle University of Thessaloniki
Outline

- Background
- Materials and Methods
- Results
- Conclusions
Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, Xu XJ, Wands JR, de la Monte SM.


Published in final edited form as:

Type 3 Diabetes is Sporadic Alzheimer’s disease: Mini-Review

Suzanne M. de la Monte
Departments of Medicine, Pathology, Neurology, and Neurosurgery, Rhode Island Hospital and the Warren Alpert Medical School of Brown University, Providence, RI
COMMON LINKS
ALZHEIMER-DIABETES
Amyloid-Tau

- Deposition of amyloid in brain and pancreatic islet cells represents a pathogenic similarity between AD and T2DM.
- Pancreatic amyloid is produced in β-cells and is coreleased with insulin.
- Islet amyloid was more frequent and extensive in AD patients than in non-AD control subjects (Janson et al., 2004).
- An increased amount of neurofibrillary tangles and amyloid plaques in the hippocampus have been found on autopsy in patients with diabetes (Peila et al., 2002).
Inflammation

- Insulin resistance, a key aspect of T2DM, is associated with inflammation in particular with elevated levels of the inflammatory markers interleukin-6 (IL-6), C-reactive protein and α-1-antichymotrypsin (Watson et al., 2003)

- IL-6 is present in senile plaques of AD patients, and elevated immunoreactivity to IL-6 is found in CSF of AD patients
Oxidative stress

• **Mitochondrial dysfunction and oxidative stress** play key roles in the pathogenesis of both diseases and represent a possible link (Moreira et al., 2007).

• There is increased oxidative stress in T2DM, with reduced antioxidant capacity.
Discovered in 1978

C-peptide in the brain of healthy subjects and AD patients

Insulin mRNA was detected in certain cerebral regions (hippocampus CA1 και CA3)
DM2 and cognitive functions

Kawamura et al. 2012
T2DM and the metabolic syndrome

- Inflammation
- Hyperinsulinemia and inhibition of IDE
- Microvascular disease
- Oxidative stress
- Advanced glycation endproducts (AGEs)

AB plaques, PHFtau tangles

- Impaired synaptic plasticity
- Synaptic degeneration
- Cell death

Inflammation

Increased GSK-3 activity
Increasing Aβ secretion
Increased inflammation
Inhibition of IDE

Brain insulin resistance

- Impaired synaptic plasticity
- Synaptic degeneration
- Cell death

Genes and environmental factors

- Inflammation
- Lipid homeostasis
- Insulin signaling

Cognitive decline and AD
Antidiabetic drugs
**PPAR-γ agonists**

- Peroxisome proliferator-activated receptor-γ plays a role in multiple processes thought to be involved in the pathogenesis of both diabetes and AD,

- including inflammatory and metabolic processes, cell growth and differentiation
Rosiglitazone prevents the memory deficits induced by amyloid-beta oligomers via inhibition of inflammatory responses

Shujun Xu, Qiao Guan, Chuang Wang, Xiaofei Wei, Xiaowei Chen, Bangxu Zheng, Pengyuan An, Junfang Zhang, Lan Chang, Wenhua Zhou, Istvan Mody*, Qinwen Wang*

Zhejiang Provincial Key Laboratory of Pathophysiology, School of Medicine, Ningbo University, Ningbo 315211, Zhejiang, China

Rosiglitazone does not improve cognition or global function when used as adjunctive therapy to AChE inhibitors in mild-to-moderate Alzheimer's disease: two phase 3 studies.


Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study.

Intranasal insulin

• Insulin is able to enter the brain within a short time via transport across olfactory and trigeminal perivascular channels and axonal pathways

• MCI patients treated with intranasal insulin (20 IU twice daily for 21 days) displayed greater improvement in memory and attention

Reger et al., 2006
• Nasal insulin spray in 240 MCI patients and mild AD patients
• 7.9 million $
• Recruitment phase
<table>
<thead>
<tr>
<th>Medication</th>
<th>Study/Year</th>
<th>Type of Study</th>
<th>Age</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Hsu et al., 2011</td>
<td>Prospective cohort</td>
<td>&gt;50 y</td>
<td>Decreased risk of dementia HR 0.76, 95% CI (0.58-0.98)</td>
</tr>
<tr>
<td>Metformin</td>
<td>Imfeld et al., 2012</td>
<td>Population based case-control</td>
<td>&gt;65 y</td>
<td>Increased risk of AD OR 1.71, 95% CI (1.12-2.60)</td>
</tr>
<tr>
<td>Metformin + Sulphonylureas</td>
<td>Hsu et al., 2011</td>
<td>Prospective cohort</td>
<td>&gt;50 y</td>
<td>Decreased risk of dementia OR 1.71, 95% CI (1.12-2.60)</td>
</tr>
<tr>
<td>Intranasal Insulin</td>
<td>Reger et al., 2008</td>
<td>RCT</td>
<td>77 y</td>
<td>Retained more functional information (p=0.01) Functional status (p=0.04)</td>
</tr>
<tr>
<td>Intranasal Insulin</td>
<td>Reger et al., 2008</td>
<td>Case-control</td>
<td>77 y</td>
<td>Improved cognition in ApoE4 negative subjects 10 IU (p=0.05), 20 IU (p=0.03), 40 IU (p=0.03)</td>
</tr>
<tr>
<td>Intranasal Insulin</td>
<td>Craft et al., 2012</td>
<td>RCT</td>
<td>74 y</td>
<td>Improved cognition (p&lt;0.05) Improved caregiver-rated functional ability (p&lt;0.01)</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Watson et al., 2005</td>
<td>RCT</td>
<td>73 y</td>
<td>Small decline in delayed recall (p=0.01)</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Risner et al., 2006</td>
<td>RCT</td>
<td>71 y</td>
<td>Improvement in cognitive status (p=0.02)</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Gold et al., 2010</td>
<td>RCT</td>
<td>72 y</td>
<td>No significant improvement in ApoE4 negative patients at 2 mg (p&lt;0.07) and 8 mg (p&lt;0.33)</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Tzimopoulou et al., 2010</td>
<td>RCT</td>
<td>72 y</td>
<td>Ameliorates impairment of brain glucose metabolism especially with ApoE4 positive subjects (p=0.02)</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Hanyu et al., 2009</td>
<td>RCT</td>
<td>77 y</td>
<td>Decrease in ADAS score at 6 months (p&lt;0.05)</td>
</tr>
<tr>
<td>Metformin + Rosiglitazone/ Glyburide</td>
<td>Ryan et al., 2006</td>
<td>RCT</td>
<td>61 y</td>
<td>Improvement in working memory Rosiglitazone (p&lt;0.001), glyburide (p=0.017)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; CI, confidence interval; AD, Alzheimer’s disease; OR, odds ratio; RCT, randomized control trial; IU, international unit; ADAS, Alzheimer’s disease assessment scale.
Aim

The aim of this current study is

• the neurophysiological and neuropsychometric assessment of the cognitive function of DM2 and MCI patients and

• the study of possible correlations and differences between the two groups
Materials and Methods

- The study participants were divided into two groups: group 1 and group 2.
- All patients underwent detailed history taking and neurological examination as part of their diagnostic work up.
- Group 1 consisted of 24 DM2 patients (7 men, 17 women; mean±SD age 70.6±6.5 years; age range 55-86 years).
- Group 2 consisted of 16 MCI patients age-matched (t=1.06, p=0.30) and gender matched ($\chi^2=0.084$, p=0.772) with the group 1 patients.
Materials and Methods-2

- All patients were assessed with auditory event-related potentials (AERPs) and neuropsychological tests, which include
  - MMSE
  - MOCA
  - IADL
  - CDR and
  - HAMILTON.

- Latencies and amplitudes of the major AERP waves (N200, P300 wave, Slow wave latency) were determined and correlations between them and the neuropsychometric test results were sought.
Results

Event related potentials

- ERP characteristics (N200, P300 wave latency and amplitude, SW latency) of groups 1 and 2 are depicted in Table 1
- No statistically significant difference was observed between the two groups (p>0.05).

Neuropsychological evaluation

- There was no statistically significant difference in all of the five neuropsychological test scores between the two groups (p>0.05)
<table>
<thead>
<tr>
<th>Test</th>
<th>Mild cognitive impairment (n=16)</th>
<th>Diabetes mellitus type2 (n=24)</th>
<th>P (M-W test)</th>
<th>P (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N200 latency</td>
<td>0.200</td>
<td>0.095</td>
<td>0.149</td>
<td>0.288</td>
</tr>
<tr>
<td>P300 latency</td>
<td>0.534</td>
<td>0.875</td>
<td>0.212</td>
<td>0.181</td>
</tr>
<tr>
<td>Slow wave latency</td>
<td>0.728</td>
<td>0.997</td>
<td>0.149</td>
<td>0.124</td>
</tr>
<tr>
<td>N200 amplitude</td>
<td>0.001</td>
<td>0.008</td>
<td>0.318</td>
<td>0.153</td>
</tr>
<tr>
<td>P300 amplitude</td>
<td>0.004</td>
<td>0.000</td>
<td>0.222</td>
<td>0.124</td>
</tr>
<tr>
<td>MMSE</td>
<td>0.104</td>
<td>0.022</td>
<td>0.521</td>
<td>0.523</td>
</tr>
<tr>
<td>MOCA</td>
<td>0.119</td>
<td>0.350</td>
<td>0.233</td>
<td>0.205</td>
</tr>
<tr>
<td>IADL</td>
<td>0.000</td>
<td>0.000</td>
<td>0.165</td>
<td>0.057</td>
</tr>
<tr>
<td>CDR</td>
<td>0.001</td>
<td>0.001</td>
<td>0.034</td>
<td>0.030</td>
</tr>
<tr>
<td>Hamilton</td>
<td>0.029</td>
<td>0.422</td>
<td>0.888</td>
<td>0.308</td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td>0.012</td>
<td>0.024</td>
<td>0.42</td>
<td>0.490</td>
</tr>
<tr>
<td>Age</td>
<td>0.831</td>
<td>0.781</td>
<td>0.229</td>
<td>0.295</td>
</tr>
</tbody>
</table>

Table 1. ERP and neuropsychometric tests scores
Conclusions

• De la Monte et al (2014) mentioned that: (i) impaired insulin signaling; (ii) insulin resistance, (iii) advanced protein glycation and oxidative stress and (iv) inflammation are potential mechanisms linking the two disorders.

• Type 2 diabetes has been associated with impairment in working memory, verbal fluency, attention and executive functions (Munshi et al., 2007, Gregg et al., 2000).
Conclusions-2

- To our knowledge, our study is the first that addresses the higher cognitive functions of DM2 and MCI patients with
  - 1. neurophysiological and
  - 2. neuropsychological markers.

- From the study results, there is evidence that the cognitive functions are affected in a similar way; a finding that supports the existence of common pathophysiological mechanisms between the two diseases.
Type 3 Diabetes

Sugar and your Brain

Is it real
This work has been supported by Archimedes III project
Thank you very much for your attention