mTOR signaling links Aβ and tau to cognitive decline: evidence from animal models

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Impact of Alzheimer’s Disease: USA

- 5.4 million people have Alzheimer’s
- 14.9 million unpaid caregivers
- 183 billion dollars in annual costs
- A new case every 69 seconds
- 6th leading cause of death

2011 Alzheimer’s Disease Facts and Figures released by the Alzheimer’s Association®
PERCENTAGE CHANGES IN SELECTED CAUSES OF DEATH (ALL AGES) BETWEEN 2000 AND 2010

Percentage

-23%  -8%  -2%  -16%  -42%

Cause of Death: Alzheimer’s disease, Stroke, Prostate cancer, Breast cancer, Heart disease, HIV

Created from data from the National Center for Health Statistics
Aβ plaques

NFTs
Genetics of Alzheimer disease

EARLY-ONSET (<5%)

1. β-Amyloid precursor protein (βAPP) (chromosome 21)
2. Presenilin 1 (PS1) (chromosome 14)
3. Presenilin 2 (PS2) (chromosome 1)

LATE-ONSET (>95%)

• Age
• The inheritance of the ε4 allele of APOE gene (chromosome 19).
PROPORTION OF PEOPLE AGE 65 AND OLDER WITH ALZHEIMER’S DISEASE AND OTHER DEMENTIAS

<table>
<thead>
<tr>
<th>Age</th>
<th>White</th>
<th>African-American</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 to 74</td>
<td>2.9%</td>
<td>9.1%</td>
<td>7.5%</td>
</tr>
<tr>
<td>75 to 84</td>
<td>10.9%</td>
<td>19.9%</td>
<td>27.9%</td>
</tr>
<tr>
<td>85+</td>
<td>30.2%</td>
<td>58.6%</td>
<td>62.9%</td>
</tr>
</tbody>
</table>

Created from data from Gurland et al.
mTOR signaling regulates protein homeostasis

Harrison et al. Nature 2009

Selman et al., Science 2009
**Experimental design**

- **3xTg-AD (n=16) on Rapamycin**
- **3xTg-AD (n=14) on control diet**
- **NonTg (n=14) on Rapamycin**
- **NonTg (n=13) on control diet**

Caccamo et al., *J Biol Chem.* 2010

Age of mice (months)

n=20/genotype/group
Morris Water Maze
3xTg-AD mice on Rapamycin

3xTg-AD mice on control food
Effects of rapamycin on learning...
...and memory
Rapamycin reduces $\text{A}\beta$ plaques
Does mTOR play a role in the diabetes/AD interaction?

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (patients with diabetes/total number of patients)</th>
<th>Relative risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ott et al. (1999)\textsuperscript{138}</td>
<td>692/6,370</td>
<td>1.9 (95% CI 1.2–3.1)</td>
</tr>
<tr>
<td>Brayne et al. (1998)\textsuperscript{139}</td>
<td>25/376\textsuperscript{†}</td>
<td>OR 1.4 (95% CI 1.1–17.0)</td>
</tr>
<tr>
<td>Yoshitake et al. (1995)\textsuperscript{140}</td>
<td>70/828</td>
<td>2.2 (95% CI 1.0–4.9)</td>
</tr>
<tr>
<td>Peila et al. (2002)\textsuperscript{98}</td>
<td>900/2,574\textsuperscript{†}</td>
<td>1.7 (95% CI 1.0–2.8)</td>
</tr>
<tr>
<td>MacKnight et al. (2002)\textsuperscript{19}</td>
<td>503/5,574\textsuperscript{†}</td>
<td>1.2 (95% CI 0.8–1.8)</td>
</tr>
<tr>
<td>Xu et al. (2004)\textsuperscript{141}</td>
<td>114/1,301</td>
<td>HR 1.3 (95% CI 0.8–1.9)</td>
</tr>
<tr>
<td>Leibson et al. (1997)\textsuperscript{142}</td>
<td>1455/75,000\textsuperscript{†}</td>
<td>SMR 1.6 (95% CI 1.3–2.0)</td>
</tr>
<tr>
<td>Luchsinger et al. (2005)\textsuperscript{143}</td>
<td>231/1,138\textsuperscript{†}</td>
<td>HR 2.4 (95% CI 1.8–3.2)</td>
</tr>
<tr>
<td>Arvanitakis et al. (2004)\textsuperscript{144}</td>
<td>27/824\textsuperscript{†}</td>
<td>HR 1.7 (95% CI 1.1–2.5)</td>
</tr>
</tbody>
</table>

Patients with probable type 2 diabetes have nearly a twofold higher risk of AD than individuals without diabetes. *Relative risk unless otherwise stated. †Data represents number of patients at follow-up, all other data represent patient numbers at baseline. Abbreviations: HR, hazard ratio; OR, odds ratio; SMR, standard morbidity ratio.
Experimental design

- CTL
- 20% Sucrose
- CTL
- 20% Sucrose + Rapamycin
- CTL

age of mice (months)
High sucrose induces obesity and peripheral insulin resistance.
Rapamycin rescues the sucrose-induced central insulin resistance...
...by decreasing mTOR signaling
Sucrose enhanced Aβ pathology by an mTOR-mediated mechanism
Summary

• Suppression of mTOR signaling reduced Ab deposits and rescued memory deficits.

• These findings further suggest that therapeutic manipulation of mTOR could be a valid approach to mitigate AD pathology.

• mTOR may represent a link between diabetes and AD.
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