Energy Failure and Mitochondrial Cascades in Alzheimer’s Disease

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Overview: Energy Metabolism in AD

• AD is associated with alterations in
  – FDG PET
  – mitochondrial enzymes
  – mtDNA
  – mitochondrial mass and maintenance

Cause versus consequence?
Possible Causal/Upstream Role?

- Energy metabolism changes with *age*
- Inter/intra tissue *selective vulnerability*
- Endophenotypes suggest *early event*
- *Histopathology* associations
- Allow for *sporadic genetics* and *lifestyle* impact
- Changes present outside the brain
Mitochondrial Cascade Hypothesis

Inheritance Determines Baseline Mitochondrial Function and Durability

Mitochondrial Function Declines with Age

A Functional Threshold is Reached

Tau Phosphorylation, Tangle Formation
Aβ Production and Plaque Deposition
Synaptic Loss And Degeneration

Swerdlow et al, BBA 1014;1842:1219-1231.
Differences in AD versus control brains also observed in AD versus control cybrid lines

- Low cytochrome oxidase Vmax activity
- Increased oxidative stress markers
- Increased Aβ
- Activated stress signaling pathways
- Reduced PGC1α mRNA
- Reduced HIF1α protein
- Activated apoptotic signaling
- NFκB activation
- Overall increased COX2 protein
- Reduced mTOR protein
- Increased mitochondrial fission
- Decreased SIRT1
- Decreased O2 consumption
- Decreased glucose utilization
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Figure. Cumulative risk of primary progressive dementia (PPD) in mothers and fathers of AD probands. By age 90, the cumulative risk of PPD is estimated to be 27.7% for mothers and 12.7% for fathers.

Maternally-Inherited AD Endophenotypes

<table>
<thead>
<tr>
<th>Endophenotype</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG PET</td>
<td>Mosconi et al, 2007; Mosconi et al, 2009</td>
</tr>
<tr>
<td>Arterial Spin Labeling</td>
<td>Okonkwo et al, 2014</td>
</tr>
<tr>
<td>Amyloid Imaging</td>
<td>Mosconi et al, 2010; Honea et al 2012</td>
</tr>
<tr>
<td>Cognition</td>
<td>Debette et al, 2009</td>
</tr>
<tr>
<td>Cytochrome Oxidase</td>
<td>Mosconi et al, 2011</td>
</tr>
</tbody>
</table>
Cytochrome Oxidase Endophenotype

Non-Synonymous mtDNA Changes in the KU ADC Cohort

Table 1. mtDNA sequencing of Clinical Cohort subjects (blood-derived mtDNA)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AD</th>
<th>CN</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Times that a SNP/mutation was overrepresented in the AD or Control group</td>
<td>16 of 23 times</td>
<td>7 of 23 times</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Times that a non-synonymous SNP/mutation was overrepresented in the AD or Control group</td>
<td>4 of 4 times</td>
<td>0 of 4 times</td>
<td></td>
</tr>
<tr>
<td>Subjects with a non-synonymous SNP/mutation</td>
<td>25/85 (29%)</td>
<td>15/170 (9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APOE4 with a non-synonymous SNP/mutation</td>
<td>20/55 (36%)</td>
<td>3/44 (7%)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>
### Table 4

Association of maternal vs paternal dementia and Alzheimer disease (AD) with baseline logical memory and visual reproduction scores, among APOE ε4 carriers

<table>
<thead>
<tr>
<th></th>
<th>Maternal dementia</th>
<th>Maternal AD</th>
<th>Paternal dementia</th>
<th>Paternal AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>159</td>
<td>159</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td>LM-d</td>
<td>$-2.18 \pm 0.64$</td>
<td>$&lt;-0.001^*$</td>
<td>$-1.82 \pm 0.70$</td>
<td>0.009$^*$</td>
</tr>
<tr>
<td>VR-d</td>
<td>$-1.86 \pm 0.57$</td>
<td>$&lt;-0.001^*$</td>
<td>$-1.75 \pm 0.63$</td>
<td>0.005$^*$</td>
</tr>
</tbody>
</table>

Apolipoprotein E

Mahley et al, PNAS 2006;103:5644-5651.


Chen et al, JBC 2011;286:5215-5221.

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Aging and the Brain

Mutational Burden vs Age

CO activity vs. age

CO activity vs. aggregate mtDNA mutational burden

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Mitochondria-Amyloid Relationships


Fukui et al. PNAS 2007;104:14163-14168

Kukreja et al. Mol Neurodegen 2014;9:16
Respiratory Flux and APP Processing

Gabuzda et al, JBC 1994;269:13623-13628.
Energy Metabolism-\(A\beta\) Nexus

Aerobic Metabolism Challenged
Limited Mitochondrial Defect
Increased Synaptic Activity
Awake

Upregulate/Increase
Aerobic Metabolism

More \(A\beta\) Production

Aerobic Metabolism De-emphasized
Profound Mitochondrial Defect
Decreased Synaptic Activity
Asleep

Downregulate/Decrease
Aerobic Metabolism

Less \(A\beta\) Production
Example of Mito-Tau Interaction

Zhao et al, Neuron 2015;87:963-975.
Predictions

• Bioenergetic changes promote Aβ in run-up to clinical AD
• Age-related pattern of up (compensated) then down (uncompensated) aerobic metabolism
• Aging to AD transition=Compensated to Uncompensated
• Translation: Enhance brain energy metabolism?
• Compensation initiates histology changes
• Biomarkers reflect brain bioenergetics/aging

Acknowledgments

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Cited investigators/Investigations


CSF Aβ42 Levels Vary With Age

APOE4 Attenuates Age-Related CSF Aβ Increase

Figure. Cerebrospinal fluid (CSF) β-amyloid 42 (Aβ42) (A) and Aβ40 (B) concentrations by age and apolipoprotein E (APOE*4) allele status in 184 normal adults aged 21 to 88 years. Closed triangles represent APOE*4-positive subjects; A = Loess-fitted line for APOE*4-positive subjects. Open circles represent APOE*4-negative subjects; B = Loess-fitted line for APOE*4-negative subjects.

ISF Aβ Correlates with Coma and Recovery

Spearman $r = 0.82$, $P<0.0001$
for $|\text{Change in GCS}| \geq 2$

Aβ: Part of a Synapse Negative Feedback Loop?

Figure 7. Negative Feedback Model Indicating Proposed Interaction between Neural Activity and APP Processing

Neural activity regulates β-secretase actions on APP. Formation of Aβ depresses synaptic transmission. Synaptic depression decreases neural activity.