The Role of Sphingolipids in Alzheimer’s Disease, Parkinson’s Disease and Lewy Body Dementia: A Common Pathway?

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Outline

- Importance of lipids in the CNS
- Sphingolipids in neurodegenerative diseases
- Link between sphingolipids, Alzheimer’s disease and pathology
- Link between sphingolipids, Parkinson’s disease and Lewy body dementia
- Ongoing research and future directions
Importance of Lipids in the CNS

- Structure of neuronal cell membranes, directly affecting the solubility and fluidity (Needham & Nunn, 1990)

- Greatly affected by oxidative stress
  - Important in brain; low anti-oxidants

- Homeostasis in neuron and myelin is a key component in preventing loss of synaptic plasticity, cell death, and ultimately, substantial neurodegeneration

- Act as second messengers
Ceramides

- Product of sphingomyelin metabolism or de novo synthesis
  - Precursor to more complex sphingolipids

- Structural role – lipid rafts

- 2nd messengers that regulate cellular differentiation, proliferation, and apoptosis
  - **Low levels**: promote cell division & play fundamental role in injury-induced cytokine production (TNF-a, IL-6)
  - **High levels**: activate signaling cascades, increase inflammation, promote free radical generation; sensitize neurons to oxidation
  - Autophagy
Sphingolipid Pathway

**Palmitoyl CoA** + **Serine**

![Pathway Diagram]

**Dihydrosphingomyelin**

**Sphingomyelin**

**Ceramide -1-PO_4**

**Sphingosine -1-PO_4**

**Ethanamine -1-PO_4** + **Hexadecenal**

**Major Depression**

**Niemann Pick Disease**

**Farber’s Disease**

**Multiple Sclerosis**

**Autoimmune Neuropathy Type 1**

**ALS?**

**Sialyl Transferase 2**

**Sialyl Transferase 3**

**GT3 Gangliosides**

**Sialyl Transferase**

**GM3 Gangliosides**

**GD3 Gangliosides**

**Lactosylceramide**

**Sialyl Transferase**

**Glucosylceramide**

**Lewy Body/PD**

**Gaucher’s Disease**

**Krabbe Disease**

**Sulfatide**

**ALS?**

**GalCer synthase**

**GalCeramidase**

**GluCer synthase**

**GluCeramidase**

**LacCer synthase**

**CST**

**ASA**

**S1P lyase**

**S1PP**

**SphK**

**CerK**

**SPT**

**3-keto-dihydrosphingosine**

**3-keto-dhSr**

**Fatty acyl CoA** + **Dihydrosphingosine**

**Sphingosine**

**Ceramide**

**Dihydroceramide**

**Sphingosine -1-PO_4**

**CerS**

**Ceramidase**

**SMase**

**SMS**

**SPT**
Ceramides-AD Neuropathology Link

• Exposure of cultured neurons to Aβ42 directly increases ceramide levels by activating neutral sphingomyelinase (nSMase) (Grimm, 2005; Jana & Pahan, 2004; Lee, 2004)
  • Inhibiting increase protects neuron from Aβ42-induced cell death (Cutler, 2004)

• Aβ42 can indirectly increase ceramides through an oxidative stress-mediated mechanism (Cutler, 2004; Matson, 2005; Gulbins & Kolesnick, 2003)

• Ceramides modulate BACE (but not gamma-secretase) activity (Kalvodova, 2005; Puglielli, 2003)

• Ceramides modulate PP2A activity, leading to tau phosphorylation (Mukhopadhyay et al., 2009)

Amyloid → PP2A → AKT dephosphorylation → Mitochondrial dysfx → Cell Death
  ↓ Ceramide
Few Human Studies Conducted

- Mixed results for ceramides & SM in brain tissues of AD patients and controls  
  (Cutler et al., 2004; Pettegrew et al., 2001)
  - SM and ceramide levels varied by disease severity  
    (Satoi et al., 2005; Han et al., 2002; Cutler et al., 2004)
  - Altered gene expression patterns of enzymes in sphingolipid metabolism pathway varied by AD severity  
    (Katsel et al., 2007)
  - Possible marker of AD progression??

- CSF ceramide and sphingomyelin levels also vary by disease severity  
  (Satoi et al., 2005; Kosicek et al., 2010; Kosicek et al., 2012)
Blood-Based Predictor of Cognitive Progression?
Overview of Blood-Based Findings

• Cognitively Normal
  • High baseline ceramides associated with increased risk of:
    • Cognitive impairment *(Mielke MM, et al., 2010a)*
    • Alzheimer’s disease *(Mielke MM, et al., 2012)*

• Mild Cognitive Impairment (MCI)
  • High baseline ceramides associated with: *(Mielke MM, et al., 2010b)*
    • Memory decline
    • Hippocampal volume loss
    • White matter integrity, primarily the posterior cingulate

• Alzheimer’s Disease
  • High baseline ceramides and SM/Cer ratios associated with:
    • Faster cognitive progression on MMSE and ADAS-Cog
      *(Mielke MM, et al., 2011)*
How do these markers relate to AD pathology?
Relationship Between Sphingolipids, Amyloid, and Tau in Humans

- **Brain**
  - *He et al., 2010* – aSMase positive correlation with amyloid and tau
  - *Katsel et al., 2007* – LASS1 & LASS2 upregulated at Braak Stage VI, LASS6 downregulated; correlation between other enzymes and Braak stage

- **CSF**
  - Previous studies did not look at relation to amyloid and tau (e.g., Satoi et al., 2005; Kosicek et al., 2012).
CSF Sphingomyelins and Tau

MCSA 70+ cognitively normal

- rho = 0.418
- p = 0.0001
- n = 88

Wisconsin 36-69 cognitively normal

- rho = 0.670
- p < 0.0001
- n = 91

Mielke MM, et al. unpublished

Next step: Mechanistic studies in Humans
Next Steps

• In vivo biomarker modeling opens up a whole new world

• Transgenic animal models primarily used for mechanistic studies, but not fully translatable

• Biomarker modeling allows for human mechanistic studies and identification of new biomarkers for given pathology and clinical phenotype
  • Clinic phenotype is heterogeneous
  • Allows for Individualized Medicine Approach
Diagram for the study of CSF and plasma sphingolipids with both clinical phenotypes and *in vivo* brain pathology.

Clinical phenotype:
- Normal Cognition
  - A+/- → N+/-
  - CSF/plasma sphingolipids

In vivo AD pathology:
- Mild Cognitive Impairment
  - A+/- → N+/-
  - Alzheimer's Disease
    - A+/- → N+

Biomarker of Interest:
- ? ? ?
  - CSF/plasma sphingolipids
  - ? ? ?
### Interactions with PiB Amyloid

<table>
<thead>
<tr>
<th>Baseline Log Plasma Ceramide</th>
<th>Change in Outcome</th>
<th>Baseline Ceramide * Time</th>
<th>Baseline Aβ * Time</th>
<th>Baseline Ceramide * Baseline Aβ * Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>b (se)</td>
<td>p-value</td>
<td>b (se)</td>
</tr>
<tr>
<td><strong>Ceramide carbon chain length or total ceramides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C14:0</td>
<td>FDG-PET</td>
<td>0.027 (0.02)</td>
<td>0.092</td>
<td>0.044 (0.02)</td>
</tr>
<tr>
<td>C16:0</td>
<td>Hippocampal volume</td>
<td>0.073 (0.10)</td>
<td>0.468</td>
<td>0.552 (0.25)</td>
</tr>
<tr>
<td></td>
<td>FDG-PET</td>
<td>0.035 (0.02)</td>
<td>0.179</td>
<td>0.158 (0.06)</td>
</tr>
<tr>
<td>C18:0</td>
<td>Hippocampal volume</td>
<td>0.194 (0.08)</td>
<td>0.015</td>
<td>0.455 (0.18)</td>
</tr>
<tr>
<td>C20:0</td>
<td>Hippocampal volume</td>
<td>0.080 (0.08)</td>
<td>0.320</td>
<td>0.490 (0.24)</td>
</tr>
<tr>
<td></td>
<td>FDG-PET</td>
<td>0.02 (0.02)</td>
<td>0.384</td>
<td>0.119 (0.06)</td>
</tr>
<tr>
<td>C24:0</td>
<td>Hippocampal volume</td>
<td>0.100 (0.08)</td>
<td>0.215</td>
<td>0.833 (0.31)</td>
</tr>
<tr>
<td></td>
<td>FDG-PET</td>
<td>0.044 (0.02)</td>
<td>0.032</td>
<td>0.160 (0.08)</td>
</tr>
<tr>
<td>C24:1</td>
<td>Hippocampal volume</td>
<td>0.838 (0.30)</td>
<td>0.005</td>
<td>0.258 (0.10)</td>
</tr>
<tr>
<td>Total</td>
<td>Hippocampal volume</td>
<td>0.104 (0.09)</td>
<td>0.240</td>
<td>1.078 (0.42)</td>
</tr>
</tbody>
</table>

*Linear mixed models adjust for age, sex, educ, APOE E4
Ceramides-AD Neuropathology Link

Amyloid $\rightarrow$ PP2A $\rightarrow$ AKT dephosphorylation $\rightarrow$ Cell Death

$\downarrow$

Ceramide
Sphingolipids, Inflammation, and AD Pathology

\[ \text{Sphingomyelin} \xrightarrow{\text{SMase}} \text{Ceramide} \]

\[ \text{TNF-\(\alpha\), IL-6} \]

<table>
<thead>
<tr>
<th>Inflammatory marker</th>
<th>(b) (95% CI)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-(\alpha)</td>
<td>-0.06 (-0.09, -0.02)</td>
<td>0.002</td>
</tr>
<tr>
<td>IL-6</td>
<td>-0.04 (-0.06, -0.01)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Models adjust for age and sex

Log SM/Cer Ratio

- Log Ceramide C24:1
- Baseline Amyloid Status=A- vs A+
- Change in HVA (per year)
- TNF-\(\alpha\)
  - Lower Tertile
  - Middle Tertile
  - Upper Tertile

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AD – Funded R01

• ~2,400 plasma samples w/corresponding imaging (PiB, FDG-PET, MRI) and/or CSF
• ~1,000 CSF

Goals: Are sphingolipids predictive of and/or associated with neurodegeneration/cognition?
  - interaction with amyloid
  - assess inflammation as effect modifier
Are Peripheral Ceramides Related to AD?

Mielke & Lyketsos, 2010
Sphingolipid Epidemiology
Participants (n = 992; 3,960 total samples) were 55 years and older and had plasma at two or more study visits over a mean of 14.3 years (range: 2.0-38.9 years). 366 women 626 men

Mielke MM, et al., 2015a
Mielke MM, et al., 2015b
Sex Differences

• Estrogen may upregulate S1P
  • Most focus is on breast cancer

• Hormone therapy reduces ceramides in pilot study

• Future step:
  • To determine association between hormones (estrogen, testosterone), sphingolipids, and risk of AD
Parkinson’s Disease (PD) and Lewy Body Dementia (LBD)
**Sphingolipid Pathway**

**Palmitoyl CoA** + **Serine**

SPT

3-keto-dihydrosphingosine

3-keto-dhSr

**Fatty acyl CoA** + **Dihydrosphingosine**

CerS

Ceramidase

3-keto-dihydrosphingosine

**Sphingomyelin**

SMase

SMS

Dihydrosphingomyelin

**Dihydroceramide**

DES

**Ceramide**

Ceramidase

**GluCer synthase**

**LacCer synthase**

**GM3 Gangliosides**

GalCer synthase

**Sialyl Transferase**

**GM3 Gangliosides**

**GT3 Gangliosides**

Sialyl Transferase 2

Sialyl Transferase 3

**GD3 Gangliosides**

**Sphingosine -1-PO4**

SphK

S1PP

**Sphingosine**

**Sphingosine -1-PO4**

S1P lyase

**Ethanolamine -1-PO4** + **Hexadecenal**
Sphingolipids in PD and LBD

• Alpha-synuclein is a lipid-binding protein; involved in the regulation of membrane lipid composition (Jo E, et al., 2000)

Ceramides

• Dopaminergic neurons positively regulate neutral sphingomyelinase activity and can cause an increase in ceramide levels (Sofic et al., 2001)

• Post-mortem and in-vitro PD studies have demonstrated that the resultant increase in ceramide levels may mediate the apoptosis observed in the substantia nigra (Hunot et al., 1997)

• Reducing ceramide levels protect against MPTP neurotoxicity (Levenson et al., 2004)
Glucosylceramides

- Glucocerebrosidase:
  - Catalyzes breakdown of glucosylceramide to ceramide + glucose
  - Glucosylceramide levels increases alpha-synuclein
  - Alpha-synuclein inhibits glucocerebrosidase activation (Mazulli et al., 2012)

- Mutations in the GBA gene coding for glucocerebrosidase:
  - ~7% of sporadic PD patients (Sidransky E, et al., 2009)
  - Most prevalent genetic mutation

- GBA mutations:
  - Higher odds of LB pathology among PD patients (Clark LN, et al., 2009)
  - Greater cognitive impairment (Brockmann K, et al., 2011; Alcalay RN, et al., 2012)
PD and LBD, cont.

- **Hypothesis:**
  - Sphingolipid metabolism (ceramides and glucosylceramides) is also affected in non-GBA mutation carriers

- **Clinical Study (Tübingen, Germany):**
  - 26 PD cognitively normal; 14 PD-MCI; 12 PDD
  - 5 controls
  - All non-GBA mutation carriers (minor/major)
<table>
<thead>
<tr>
<th>Log Lipid</th>
<th>PD-NC (N=26) Median (range)</th>
<th>PD-MCI/PDD (N=26) Median (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ceramide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C16:0</td>
<td>11.48 (10.93, 12.26)</td>
<td>11.67 (11.27, 12.79)</td>
<td>0.035</td>
</tr>
<tr>
<td>C18:0</td>
<td>10.98 (10.24, 12.24)</td>
<td>11.18 (10.44, 12.54)</td>
<td>0.016</td>
</tr>
<tr>
<td>C20:0</td>
<td>12.21 (11.32, 13.58)</td>
<td>12.54 (11.80, 14.10)</td>
<td>0.037</td>
</tr>
<tr>
<td>C22:0</td>
<td>13.63 (12.83, 14.77)</td>
<td>13.94 (12.67, 16.14)</td>
<td>0.037</td>
</tr>
<tr>
<td>C24:0</td>
<td>15.73 (14.37, 16.85)</td>
<td>16.01 (14.17, 18.00)</td>
<td>0.621</td>
</tr>
<tr>
<td>C26:0</td>
<td>11.94 (9.68, 12.84)</td>
<td>12.15 (9.70, 14.07)</td>
<td>0.510</td>
</tr>
<tr>
<td>C22:1</td>
<td>9.86 (8.83, 10.60)</td>
<td>9.95 (9.43, 11.92)</td>
<td>0.442</td>
</tr>
<tr>
<td>C24:1</td>
<td>13.23 (12.34, 14.83)</td>
<td>13.44 (12.67, 15.32)</td>
<td>0.048</td>
</tr>
<tr>
<td>C26:1</td>
<td>9.70 (8.46, 11.05)</td>
<td>9.90 (8.87, 11.77)</td>
<td>0.380</td>
</tr>
<tr>
<td><strong>Monohexosylceramides (Glucosyl- &amp; Galactosylceramides)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C16:0</td>
<td>11.92 (11.03, 12.79)</td>
<td>12.09 (11.35, 14.29)</td>
<td>0.046</td>
</tr>
<tr>
<td>C18:0</td>
<td>9.11 (8.40, 10.15)</td>
<td>9.15 (8.33, 10.80)</td>
<td>0.242</td>
</tr>
<tr>
<td>C20:0</td>
<td>10.48 (9.79, 11.31)</td>
<td>10.72 (10.07, 12.11)</td>
<td>0.039</td>
</tr>
<tr>
<td>C22:0</td>
<td>13.75 (12.97, 14.61)</td>
<td>13.95 (13.18, 15.52)</td>
<td>0.148</td>
</tr>
<tr>
<td>C24:0</td>
<td>14.17 (13.15, 15.49)</td>
<td>14.56 (13.26, 16.31)</td>
<td>0.040</td>
</tr>
<tr>
<td>C26:0</td>
<td>10.20 (8.82, 11.16)</td>
<td>10.23 (8.17, 12.28)</td>
<td>0.840</td>
</tr>
<tr>
<td>C16:1</td>
<td>9.50 (8.67, 9.99)</td>
<td>9.58 (9.12, 11.72)</td>
<td>0.089</td>
</tr>
<tr>
<td>C22:1</td>
<td>9.94 (9.02, 10.59)</td>
<td>10.00 (9.00, 11.88)</td>
<td>0.370</td>
</tr>
<tr>
<td>C24:1</td>
<td>10.02 (8.48, 11.06)</td>
<td>10.09 (9.26, 12.48)</td>
<td>0.272</td>
</tr>
</tbody>
</table>

*Note: The data for monohexosylceramides (Glucosyl- & Galactosylceramides) is marked with an asterisk (*) to indicate a different type of molecule from the ceramides listed above.
**Sphingolipid Pathway**

- **Palmitoyl CoA** + **Serine**
  - SPT → **3-keto-dihydrosphingosine**
  - **Fatty acyl CoA** + **Dihydrosphingosine**
    - **Ceramide**
    - **Sphingosine**
  - **Dihydrosphingomyelin**
  - **Sphingomyelin**
  - **Ceramide -1-PO₄**
  - **Ceramide -1-PO₄**
  - **Ethanolamine -1-PO₄** + **Hexadecenal**

- **GluCer synthase** → **Glucosylceramide**
- **GalCer synthase** → **Galactosylceramide**
- **S1P lyase** → **Sphingosine -1-PO₄**
- **S1P lyase** → **Sphingosine -1-PO₄**
- **CerS Ceramidase**
- **CerK**
- **C1PP**

- **Lewy Body/PD**
- **Isomers**
- **GM3 Gangliosides**
- **GD3 Gangliosides**
- **GT3 Gangliosides**

- **Sulfatide**
  - ASA → **CST**
  - **GalCer synthase**
  - **GalCer amidase**

- **Levy Body/PD**
- **Sialyl Transferase**
  - **Sialyl Transferase 2**
  - **Sialyl Transferase 3**
Ceramides, Glucosylceramides and PD

• Aims:
  • To replicate the previous cross-sectional study
  • To determine whether the lipids predict cognitive decline
  • To further explore GBA mutations and cognitive impairment in PD
### Baseline Characteristics (N=412)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PD-NC (N=272)</th>
<th>PD-MCI (N=85)</th>
<th>PDD (N=55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline age</td>
<td>66.2 (8.2)</td>
<td>67.8 (7.0)</td>
<td>72.4 (4.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>5.9 (4.9)</td>
<td>7.6 (5.7)</td>
<td>9.3 (6.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>188 (69.1%)</td>
<td>55 (64.7%)</td>
<td>55 (69.1%)</td>
<td>0.750</td>
</tr>
<tr>
<td>Education: University</td>
<td>188 (70.2%)</td>
<td>59 (70.2%)</td>
<td>41 (74.6%)</td>
<td>0.802</td>
</tr>
<tr>
<td>BMI</td>
<td>26.7 (4.2)</td>
<td>26.7 (4.1)</td>
<td>26.5 (4.9)</td>
<td>0.895</td>
</tr>
<tr>
<td>UPDRS I</td>
<td>1.7 (1.7)</td>
<td>2.4 (1.7)</td>
<td>5.2 (2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>20.8 (11.0)</td>
<td>24.9 (11.3)</td>
<td>30.6 (12.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GDS</td>
<td>3.0 (2.6)</td>
<td>2.9 (2.7)</td>
<td>6.4 (3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AES</td>
<td>28.6 (7.9)</td>
<td>29.3 (2.7)</td>
<td>39.5 (10.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PANDA</td>
<td>21.0 (5.2)</td>
<td>16.0 (5.1)</td>
<td>9.3 (4.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PDQ-39</td>
<td>22.0 (13.6)</td>
<td>24.9 (12.5)</td>
<td>39.3 (14.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.6 (1.5)</td>
<td>27.9 (1.9)</td>
<td>24.4 (3.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PD-NC (N=272)</th>
<th>PD-MCI (N=85)</th>
<th>PDD (N=55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any GBA mutation</td>
<td>41 (15.3%)</td>
<td>19 (22.6%)</td>
<td>20 (37.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pathogenic GBA mutation</td>
<td>6 (2.2%)</td>
<td>2 (2.4%)</td>
<td>6 (11.1%)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

BMI = body mass index; UPDRS = Unified Parkinson’s Disease Rating Scale; GDS = Geriatric Depression Scale; AES = Apathy Evaluation Scale; PANDA = Parkinson Neuropsychometric Dementia Assessment; PDQ = Parkinson’s Disease Questionnaire; MMSE = Mini-Mental Status Examination
All PD patients

Cognitively Normal PD patients

Log Sphingosine/Glucosylsphinosine ratio

Hoehn & Yahr Scale

Hoehn & Yahr Scale
A higher ceramide to glc-Cer ratio is associated with greater cognitive decline among cognitively normal patients with Parkinson’s disease.

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Without GBA mutations/variants (N=194)</th>
<th>With GBA mutations/variants (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Association between one log unit increase in the baseline ratio and one-year change in MMSE</td>
<td>Association between one log unit increase in the baseline ratio and one-year change in MMSE</td>
</tr>
<tr>
<td></td>
<td>cross-sectional</td>
<td>MMSE</td>
</tr>
<tr>
<td>Ratio</td>
<td>b</td>
<td>p-value</td>
</tr>
<tr>
<td>C16:0</td>
<td>0.94</td>
<td>0.151</td>
</tr>
<tr>
<td>C18:0</td>
<td>0.86</td>
<td>0.099</td>
</tr>
<tr>
<td>C18:1</td>
<td>0.04</td>
<td>0.906</td>
</tr>
<tr>
<td>C20:0</td>
<td>0.48</td>
<td>0.336</td>
</tr>
<tr>
<td>C22:0</td>
<td>0.87</td>
<td>0.102</td>
</tr>
<tr>
<td>C24:0</td>
<td>0.58</td>
<td>0.296</td>
</tr>
<tr>
<td>C24:1</td>
<td>0.35</td>
<td>0.493</td>
</tr>
<tr>
<td>Sph</td>
<td>0.21</td>
<td>0.334</td>
</tr>
</tbody>
</table>

*Association between each log-unit increase in baseline ceramide to glc-Cer and sphingosine to glc-Sph ratios and cross-sectional and one-year change in MMSE score
ADRC pilot project

- **Aim 1**: Comparison of 40 DLB, 12 MCI+RBD, 17 iRBD and 70 age- and sex-matched cognitively normal individuals

- **Aim 2**: Cross-sectional association between the lipids and neuroimaging
  - Dorsal mesopontine gray matter atrophy; occipital hypometabolism
  - Stratify by Amyloid status

- **Aim 3**: Determine whether the lipids predict disease progression
Ceramides elevated in DLB and iRBD versus matched controls

<table>
<thead>
<tr>
<th>lipid</th>
<th>DLB vs. control (N=40/group)</th>
<th>iRBD vs. control (n=17/group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>p-value</td>
</tr>
<tr>
<td>s1p</td>
<td>-0.018</td>
<td>0.557</td>
</tr>
<tr>
<td>cer C14:0</td>
<td>-0.0001</td>
<td>0.916</td>
</tr>
<tr>
<td><strong>cer C16:0</strong></td>
<td><strong>0.056</strong></td>
<td><strong>0.029</strong></td>
</tr>
<tr>
<td>cer C18:1</td>
<td>0.001</td>
<td>0.476</td>
</tr>
<tr>
<td>cer C18:0</td>
<td>0.016</td>
<td>0.265</td>
</tr>
<tr>
<td>cer C20:0</td>
<td>0.014</td>
<td>0.313</td>
</tr>
<tr>
<td>cer C22:0</td>
<td>0.040</td>
<td>0.142</td>
</tr>
<tr>
<td><strong>cer C24:1</strong></td>
<td><strong>0.135</strong></td>
<td><strong>0.046</strong></td>
</tr>
<tr>
<td>cer C24:0</td>
<td>0.047</td>
<td>0.590</td>
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</tbody>
</table>
Higher plasma ceramides associated with lower grey matter mesopontine volume among iRBD

<table>
<thead>
<tr>
<th>lipid</th>
<th>iRBD (N=16)</th>
<th></th>
<th></th>
<th>iRBD A- (N=12)</th>
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<tbody>
<tr>
<td>sph</td>
<td>-54.26</td>
<td>0.492</td>
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<td>60.65</td>
<td>0.560</td>
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<tr>
<td>spa</td>
<td>-223.91</td>
<td>0.354</td>
<td></td>
<td>-157.65</td>
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<tr>
<td>cer C14:0</td>
<td>-711.52</td>
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<td>-697.79</td>
<td>0.012</td>
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<tr>
<td>cer C16:0</td>
<td>-16.26</td>
<td>0.069</td>
<td></td>
<td>-18.99</td>
<td>0.038</td>
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</tr>
<tr>
<td>cer C18:1</td>
<td>-465.63</td>
<td>0.047</td>
<td></td>
<td>-577.93</td>
<td>0.006</td>
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<tr>
<td>cer C18:0</td>
<td>-44.88</td>
<td>0.003</td>
<td></td>
<td>-46.29</td>
<td>0.005</td>
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<tr>
<td>cer C20:0</td>
<td>-33.30</td>
<td>0.049</td>
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<td>-34.78</td>
<td>0.059</td>
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<tr>
<td>cer C22:0</td>
<td>-9.43</td>
<td>0.321</td>
<td></td>
<td>-1.17</td>
<td>0.911</td>
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</tr>
<tr>
<td>cer C24:1</td>
<td>-9.45</td>
<td>0.002</td>
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<td>-8.97</td>
<td>0.022</td>
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</tr>
<tr>
<td>cer C24:0</td>
<td>-0.37</td>
<td>0.900</td>
<td></td>
<td>2.22</td>
<td>0.451</td>
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</tr>
</tbody>
</table>
PD Ongoing Research

• Predict PD progression
  • 500 PD patients (normal cognition, MCI, PDD).
  • Ceramides and glycosylceramides at baseline
  • Lipid levels associated with & predictive of cognitive decline (and other outcomes)

• Comparison of PD GBA mutation carriers, PD sporadic non-carriers, normal controls
  • CSF and plasma ceramides and glucosylceramides

• Comparison of DLB, MCI+RBD, iRBD and age- and sex-matched cognitively normal individuals
  • CSF and plasma ceramides and glucosylceramides
Conclusion

• Consistent evidence for role of ceramide metabolism in AD, LBD, and other neurodegenerative diseases
  • Animals and humans
  • CSF and plasma

• Common pathway; Different forks in the road?

• Identification in blood – blood-based biomarkers?

• Collaborative, translational effort needed
  • Better understanding of ceramides and AD/LBD pathology in animals
  • Roles of exosomes, ceramide transporters (CERT)
  • Better understanding and characterization of sphingolipid levels in the population and relation to disease pathology (direct vs. indirect)
Collaborators & Funding

Mayo Clinic
• Bradley Boeve, MD
• Dennis Dickson, MD
• Clifford Jack, MD
• K. Sree Nair, MD
• Ronald Petersen, MD, PhD
• Walter Rocca, MD, MPH
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• Constantine Lyketsos, MD

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• Krista Lanctôt, PhD

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• Walter Maetzler, MD

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Call for Papers:

Special Issue – Sphingolipids in Neurodegeneration Diseases

Journal of Alzheimer’s Disease

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Thank You!

Questions & Discussion