Diet, Exercise, NSAIDs, and Inclusion Body Myositis

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What is AD?

- **Aging**
- **Pathogenic Mutations**
- **Diet & Metabolism**
- **Genetic Modifiers**

Alteration of Aβ Production and/or Clearance

Toxic Aβ Oligomer

Plaques

Tangles

Alzheimer’s Disease
Amyloid Precursor Protein and β-Amyloid

sAPP-β

sAPP-α

Aβ region

β-secretase

α-secretase

γ-secretase

Extracellular

Intracellular

APP

C83

AICD

Amyloidogenic Processing (~10%)
Is AD a loss of Repression on the Aβ Producing Enzymes?

**Normal Aging**

β-Secretase

γ-Secretase

Aβ

Healthy Brain

**Pathologic Aging**

β-Secretase

γ-Secretase

Aβ

Alzheimer's Disease
Amyloid Pathology is Generic


- AD (Plaque)
- FTD (Tangle)
- PD (Lewy Body)
- HD (Nuclear Inclusion)
- ALS (Cytoplasm Inclusion)
- CJD (PrPs Plaques)
IBM and AD

- In the brain of AD patients the Aβ forms plaques that are *outside* of the cells.

- In the muscle of IBM patients the Aβ forms inclusions that are *inside* of the cells.
Connection…?

1) Aβ-positive, non-congophilic deposits appear prior to frank vacuolization in IBM affected muscle fibers

2) mRNA for APP, the larger protein from which Aβ is derived, is increased in sIBM, as is the APP protein itself

3) β-secretase, a major amyloidogenic enzyme involved in AD, is up regulated in IBM (as well as in AD and aging in general)

4) Overexpression of APP and/or APP fragments containing Aβ in the muscle of transgenic mice leads to degenerative changes similar to the disease state in humans
One of the only options to resolve the actual role of Aβ in the disease process, is to perform experiments in animal models.

IBM-T7A6 mouse: reported in 2002 in collaboration with Frank LaFerla, UCI

Overexpresses full-length APP in muscle under the direction of a creatine kinase promoter
What is sIBM?

Pharmacology and Genetics

NSAIDs

APP Transgenic

APP Knock-In

Lifestyle Interventions

Exercise

Diet
Exercise

- Nice resonance for a muscle disease
- Several anecdotal reports indicate that moderate exercise may help IBM patients
- Simple running wheel activity reduces pathology in several mouse models of AD
- However, minimal effect in sIBM mice
Mice do get a little better in muscle function, but NO effect on the underlying pathology.
NSAIDs

- **Aβ42** [pmol/mg protein]
  - WT
  - TG
  - Control Diet
  - Ibuprofen
  - Naproxen
  - Carprofen
  - R-Flurbiprofen

- **Total COX** [umol/min/mg]
  - WT
  - TG
  - Control Diet
  - Ibuprofen
  - Naproxen
  - Carprofen
  - R-Flurbiprofen

- **Latency to Fall** (sec)
  - WT
  - TG
  - Control Diet
  - Ibuprofen
  - Naproxen
  - Carprofen
  - R-Flurbiprofen

**H&E**
- WT Control
- TG Control
- Ibuprofen
- Naproxen
- Carprofen
- R-Flurbiprofen

**Gomori Trichrome**
- WT Control
- TG Control
- Ibuprofen
- Naproxen
- Carprofen
- R-Flurbiprofen

**AI (4G8)**
- WT Control
- TG Control
- Ibuprofen
- Naproxen
- Carprofen
- R-Flurbiprofen
Other Mice?

A. 

**Brain**

![Graph showing Aβ peptide levels in different genotypes](image)

**Muscle**

![Graph showing Aβ peptide levels in different genotypes](image)

**Genotype (~2 Months Old)**

- APP
- PS1
- P264L
- ΔNL
- ΔNL
- ΔNL
- ΔNL

B. 

**Brain Aβ Peptide (fmol/mL)**

- DEA
- SDS
- FA

![Graph showing Aβ peptide levels in different stages](image)

**APPΔNL x PS1P264L Age (Months)**

- 3 Months
- 6 Months
- 9 Months
- 12 Months

C. 

![Images of tissue samples at different stages](image)
<table>
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<th>Aβ</th>
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<tr>
<td>Diet</td>
<td>-</td>
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