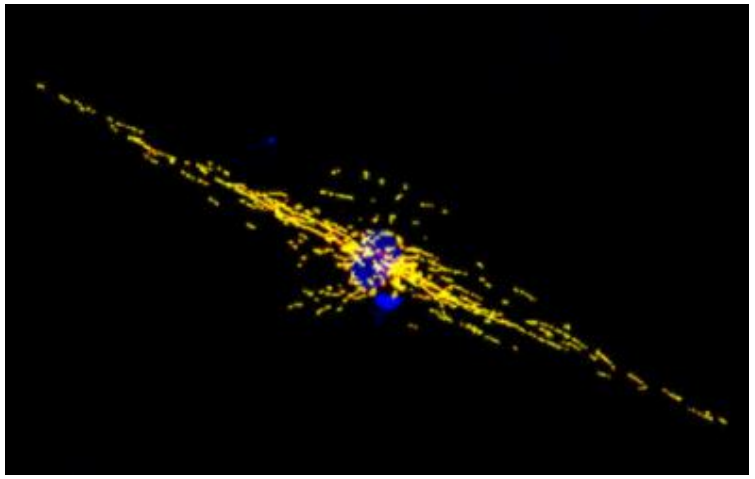
Bioenergetics and the Brain: Unlocking the Mitochondrial Connection to Dementia



Heather Wilkins, PhD
Associate Professor, Department of Neurology
Co-director, Biomarker Core
University of Kansas Alzheimer's Disease Research Center

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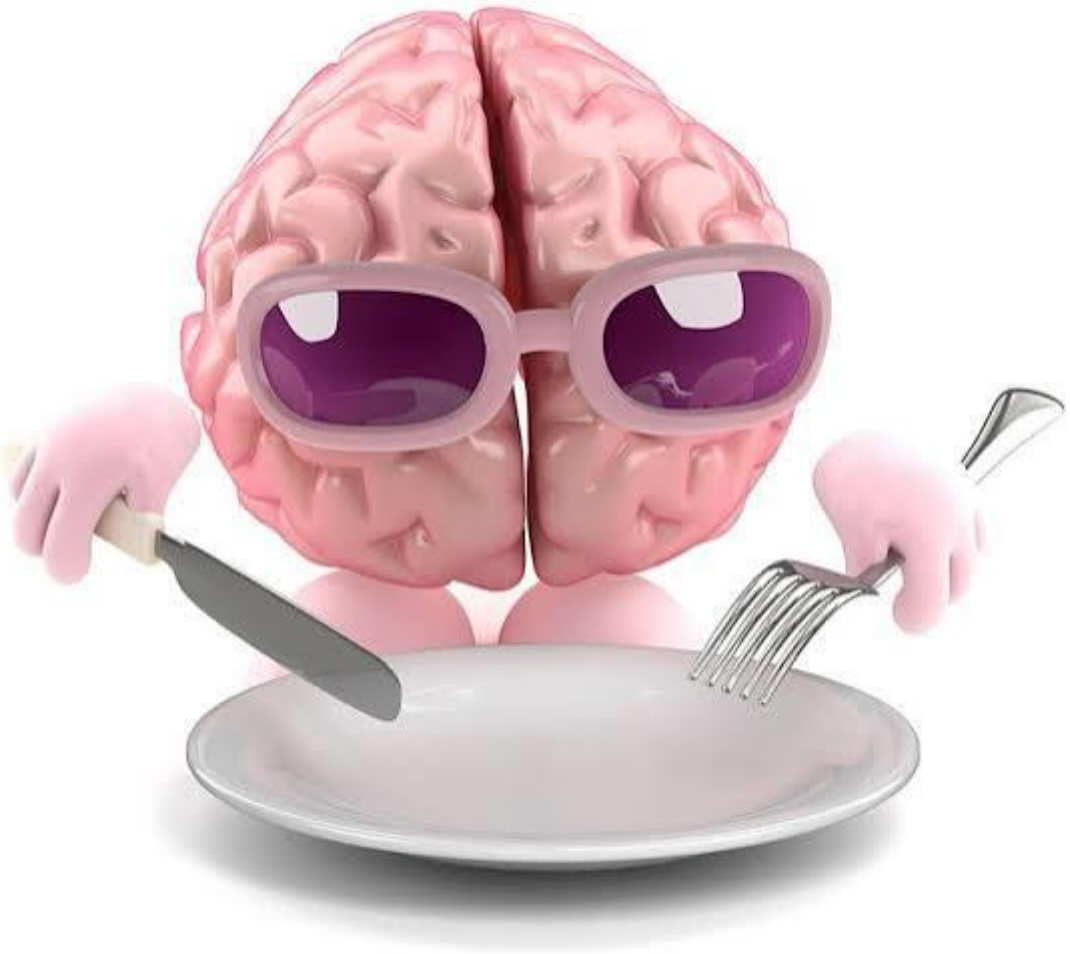
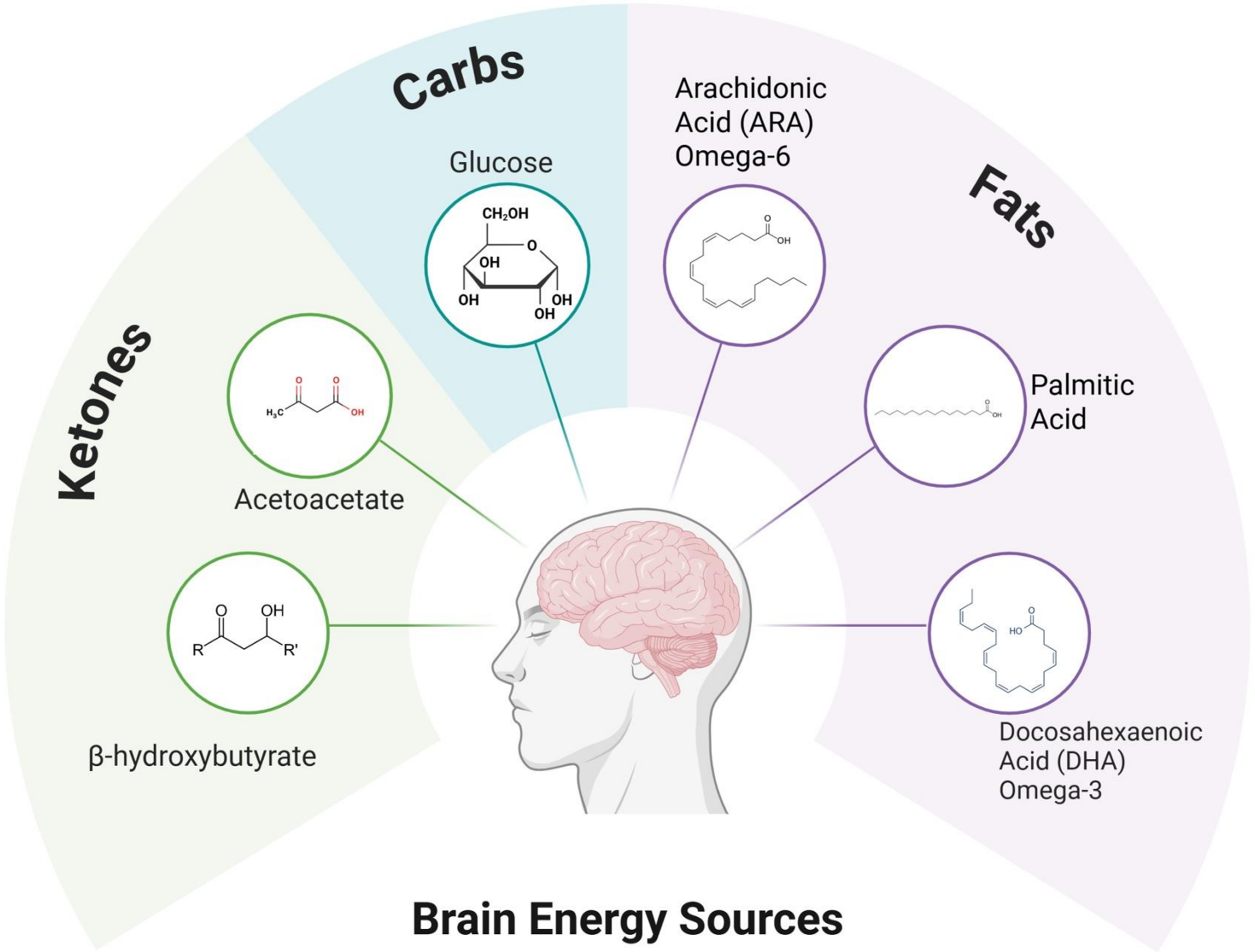
The Brain is Greedy!

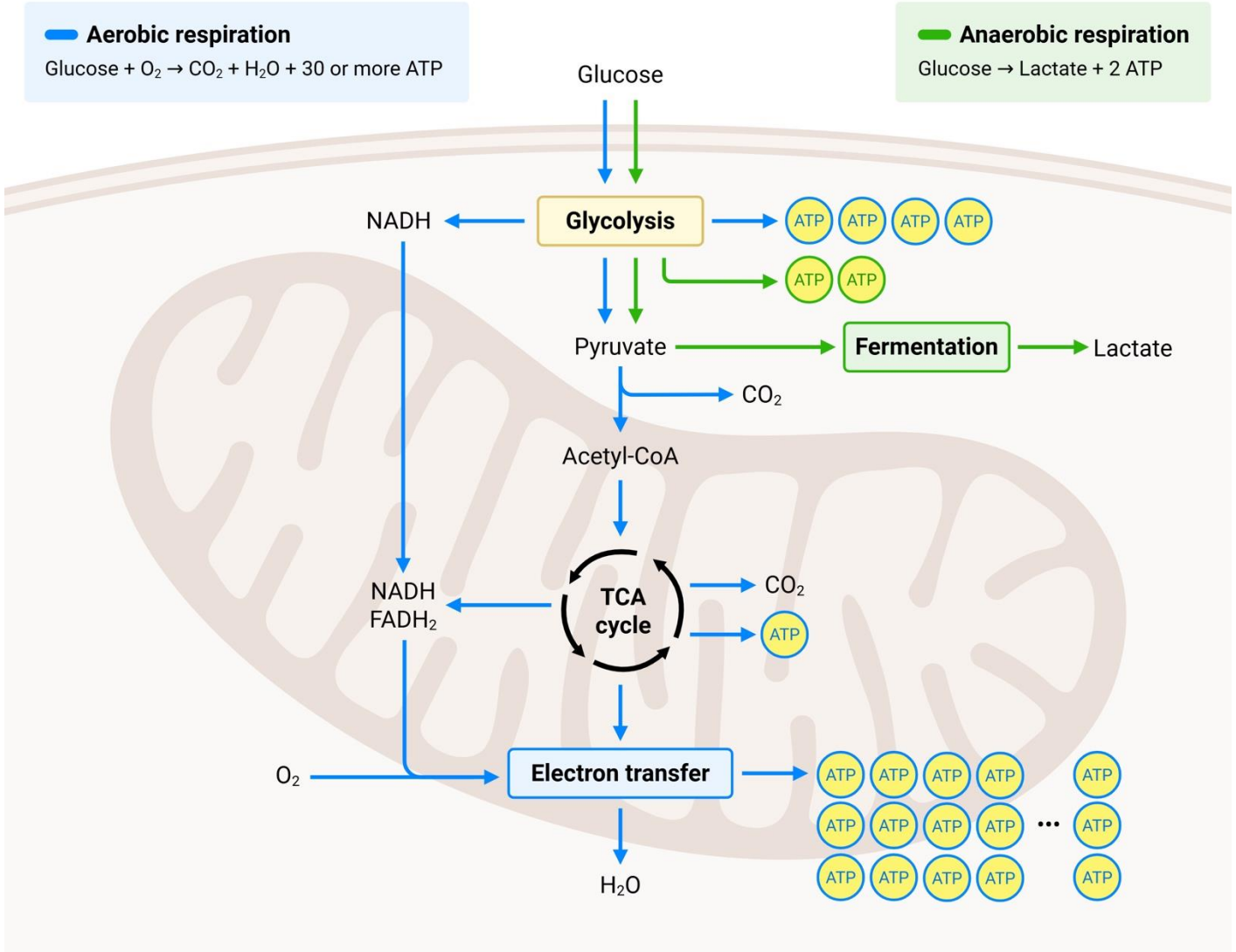


- The brain is only 2% of total body weight but consumes 20% of the body's total oxygen
- Large amounts of energy are needed for brain function
  - ***Cognition/memory!!***

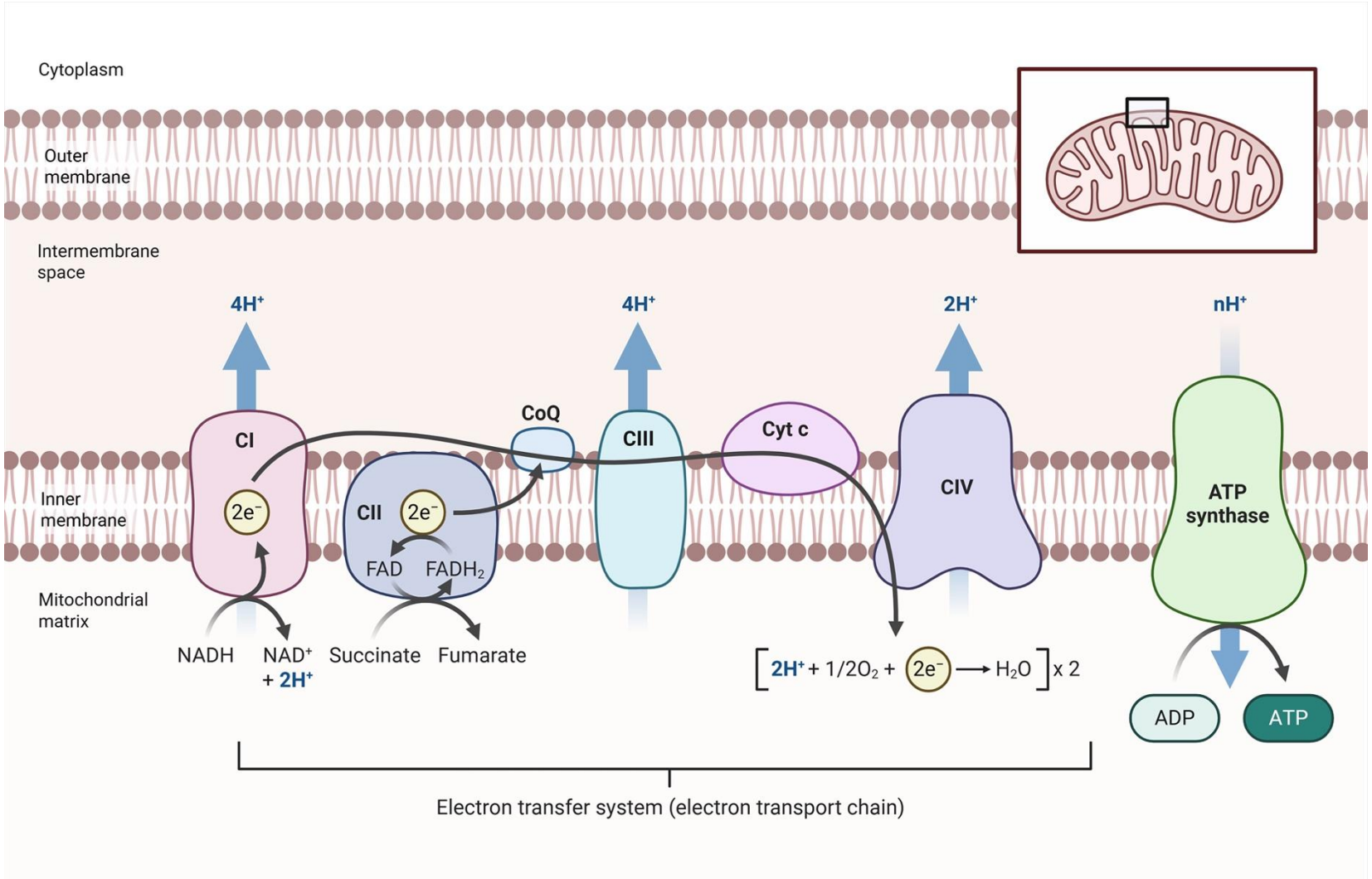
The Brain Can Use Many Different Fuel Sources



Bioenergetics and Mitochondria



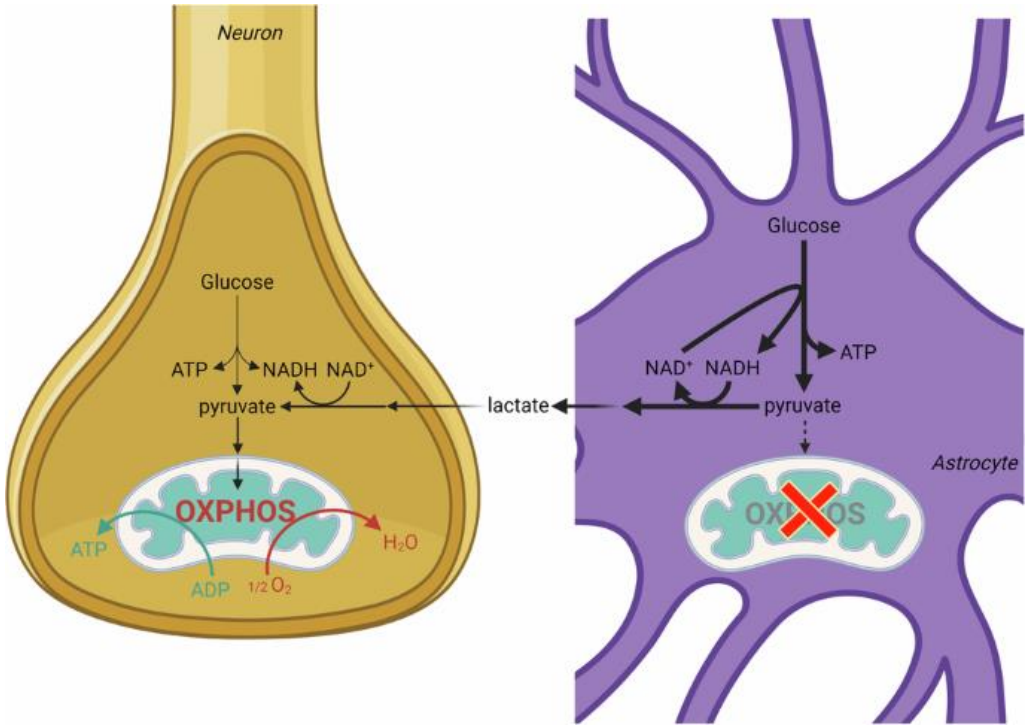
Bioenergetics and Mitochondria



Brain Energy Metabolism is Diverse

Neurons and Astrocytes are coupled through energy metabolism

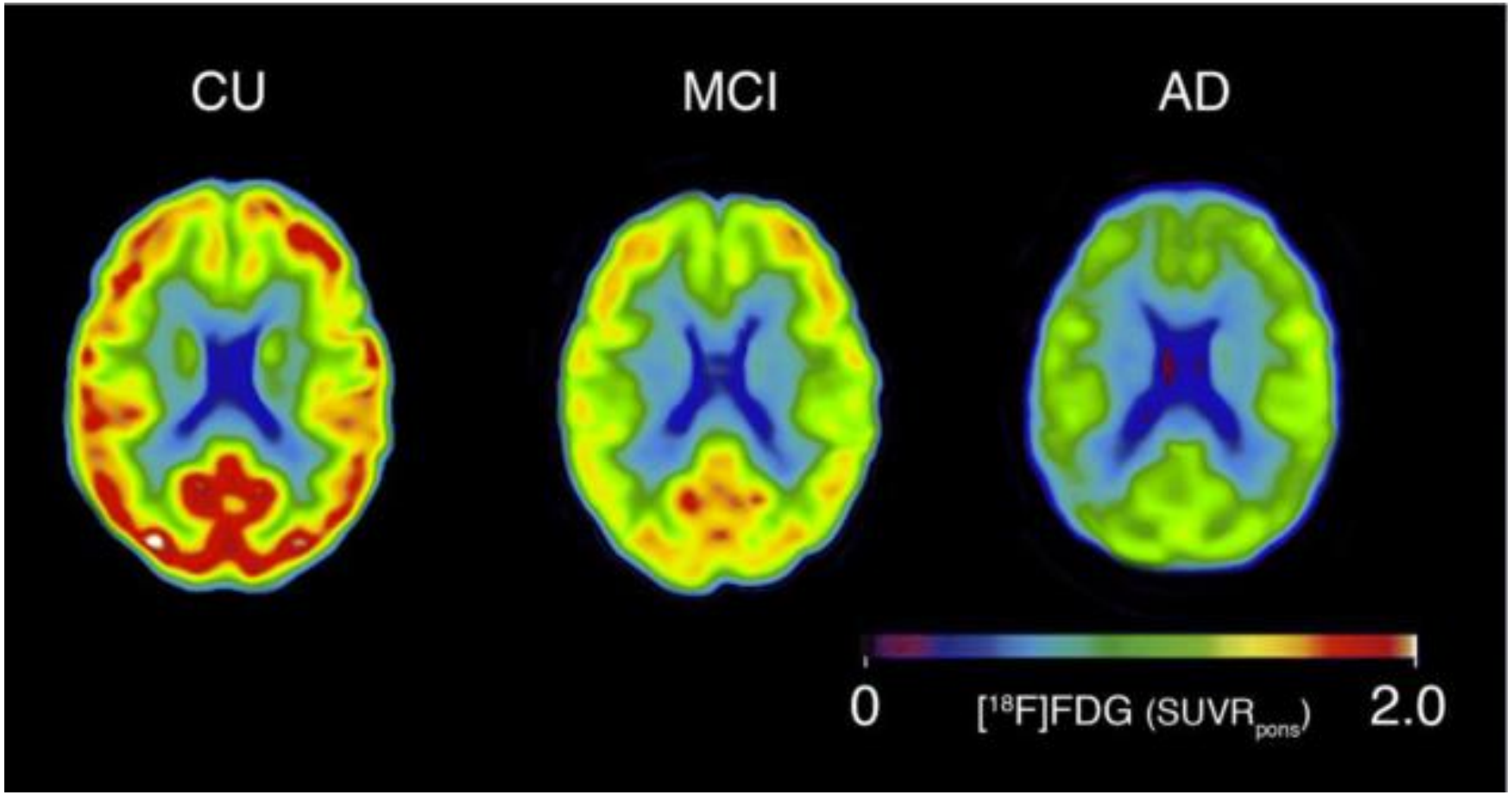
- Neurons rely on mitochondrial metabolism (oxidative phosphorylation)
- Astrocytes rely on glycolysis (glucose)
- Neurons have low fatty acid metabolism while astrocytes have high fatty acid metabolism



Is this to prevent competition?

PMID: 39181993

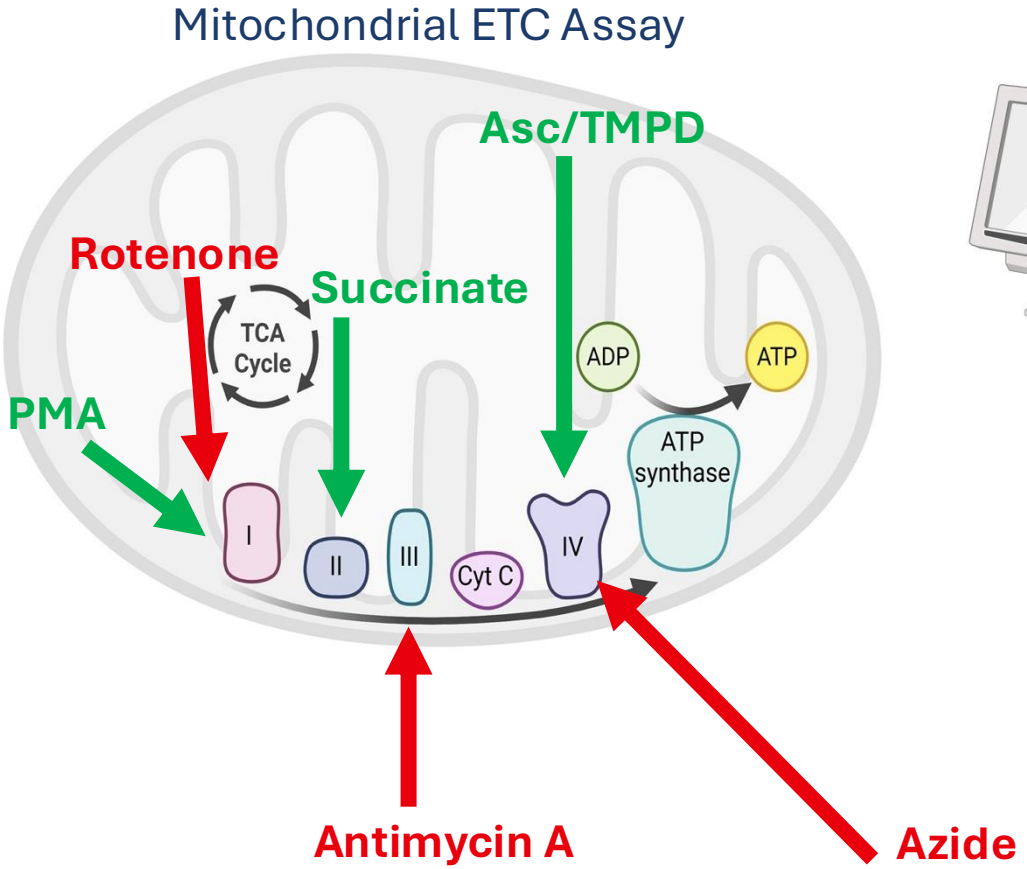
Why Do We Care About Brain Energy Metabolism in Alzheimer's Disease?

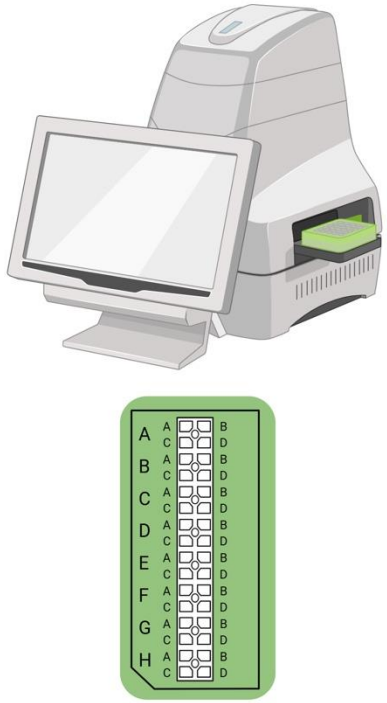


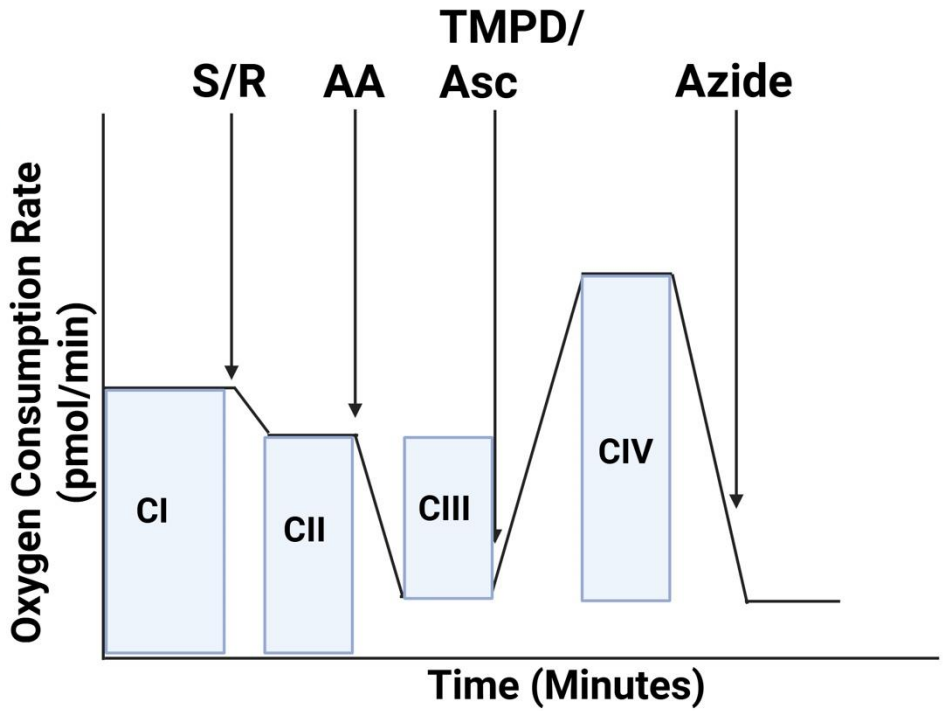
CU=Cognitively unaffected
MCI=Mild Cognitive Impairment
AD=Alzheimer's Disease

https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet
PMID: 20083042, 32885024, 34276532

How do we measure mitochondrial function?

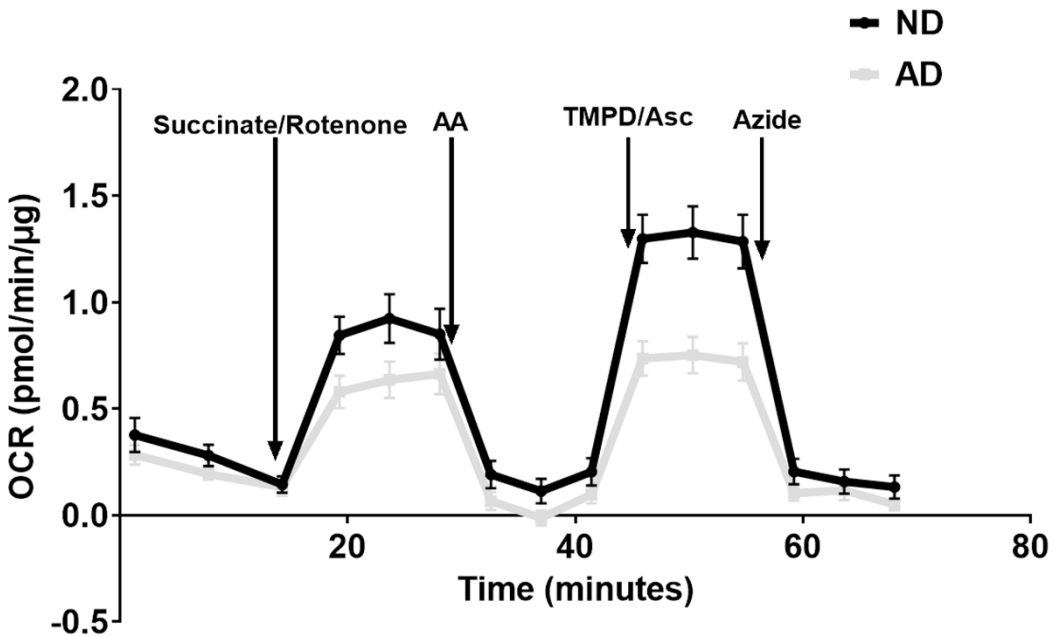


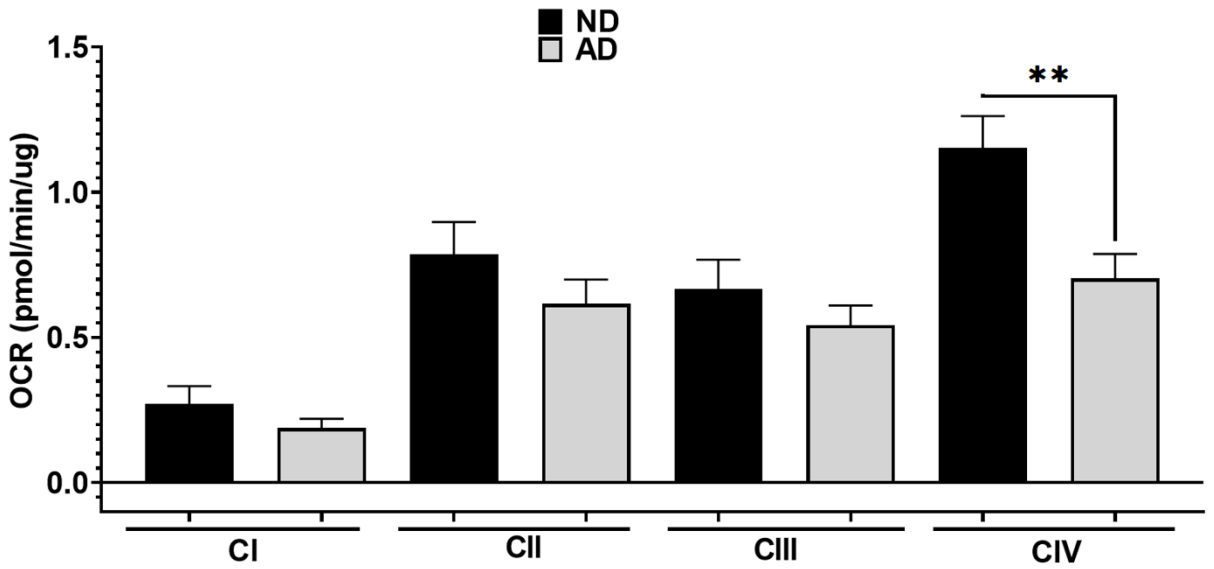




Mitochondria are dysfunctional in Alzheimer's Disease

Human Brain (postmortem)





11 ND versus 12 AD

PMID: 35667615, 37614699

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ND=non demented
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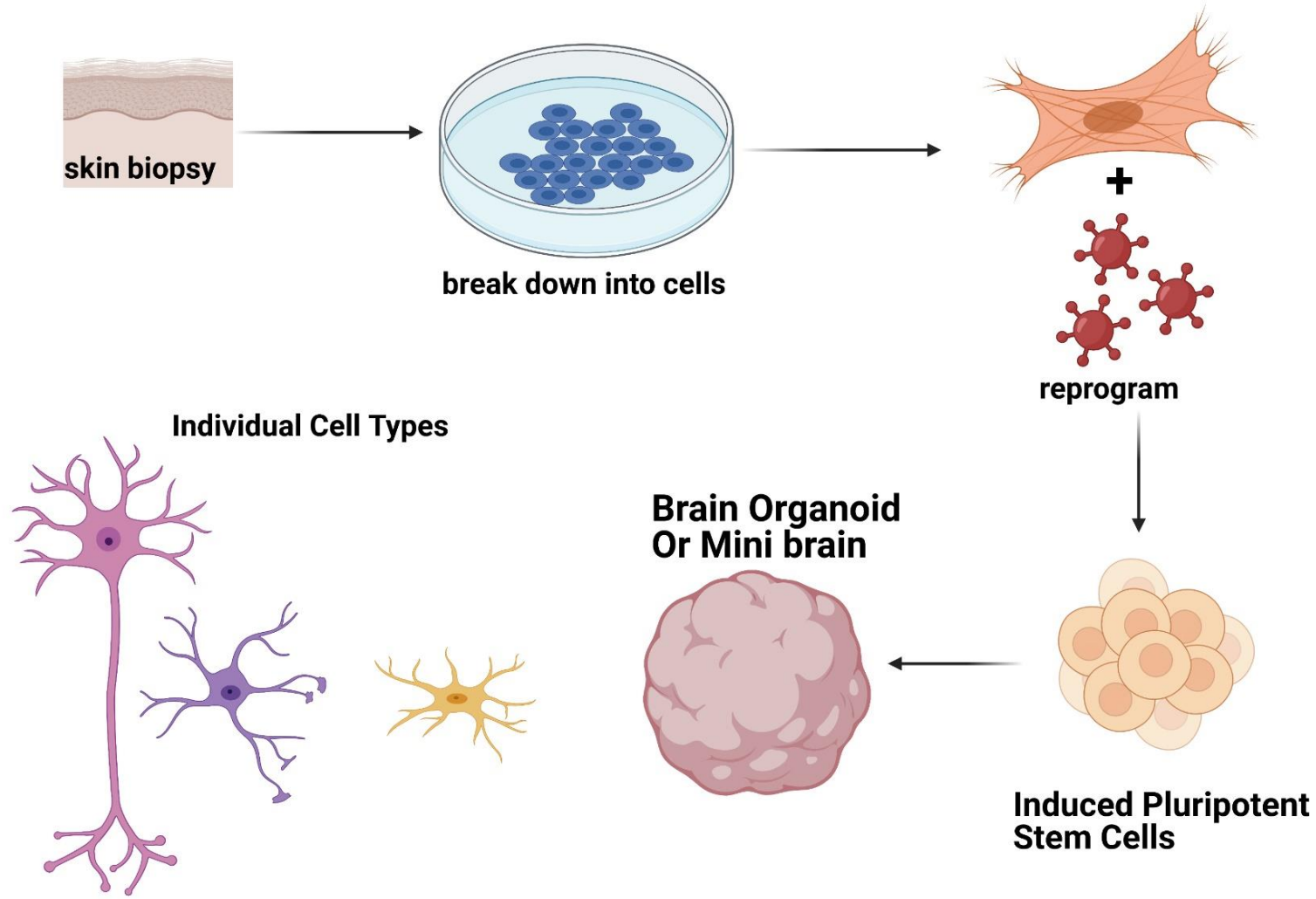
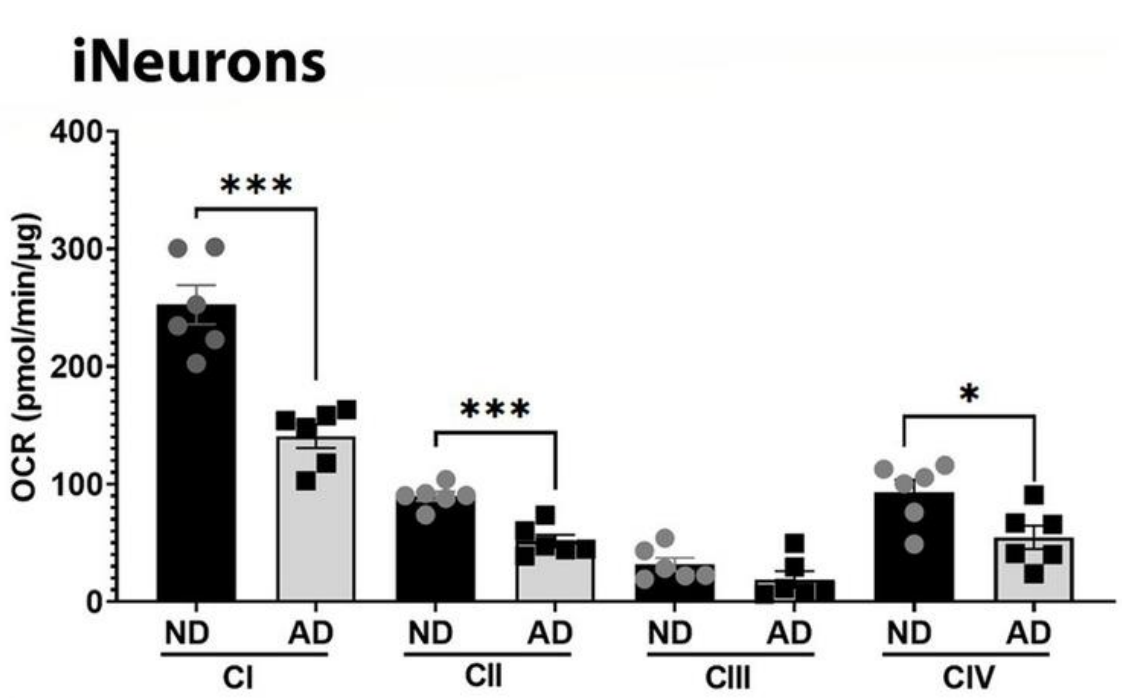
How do we measure mitochondrial function?

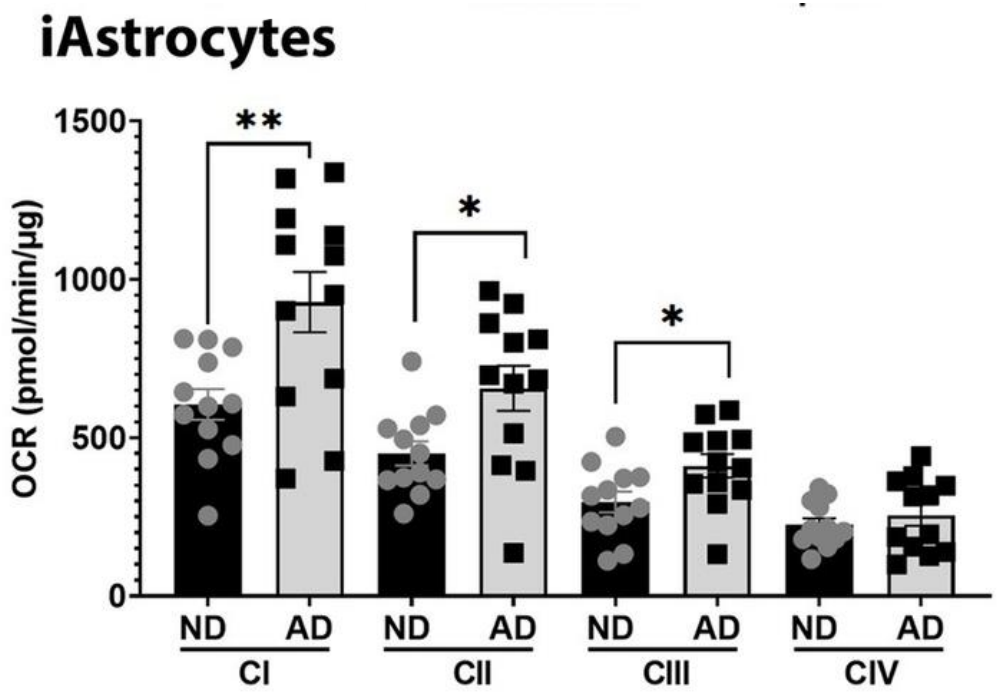
Induced Pluripotent Stem Cell Models



Created with BioRender

Neurons and Astrocytes Differ in Mitochondrial Function with AD





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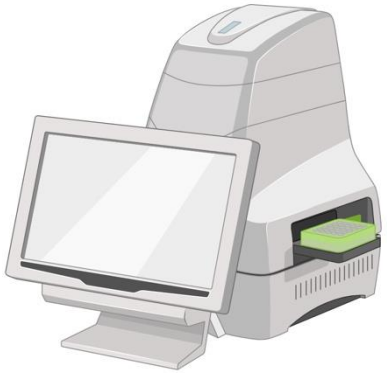
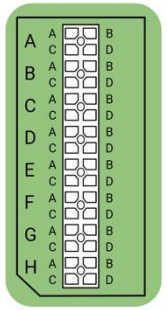
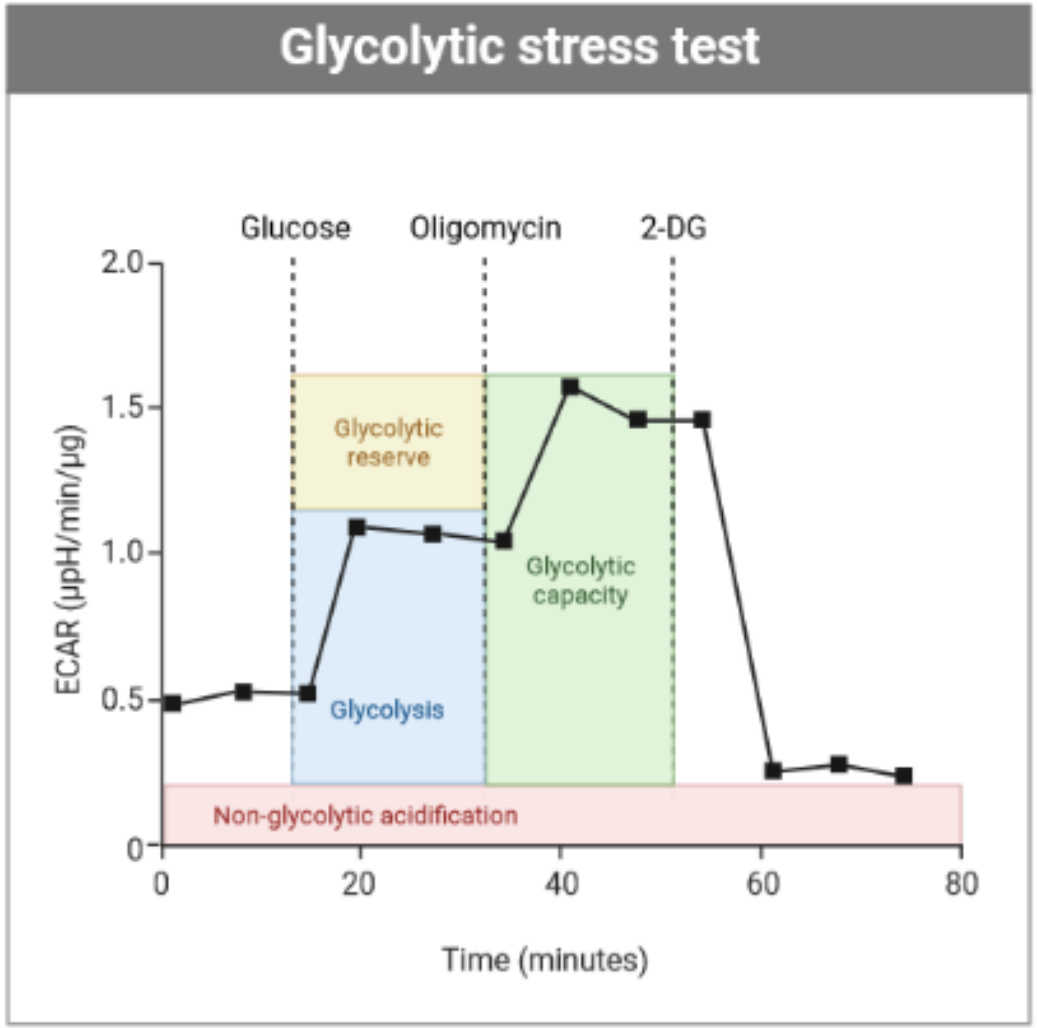
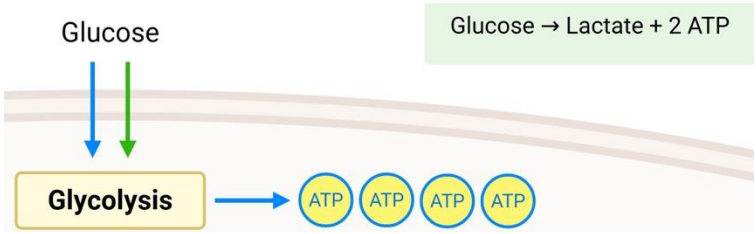
How Do We Measure Glycolysis?

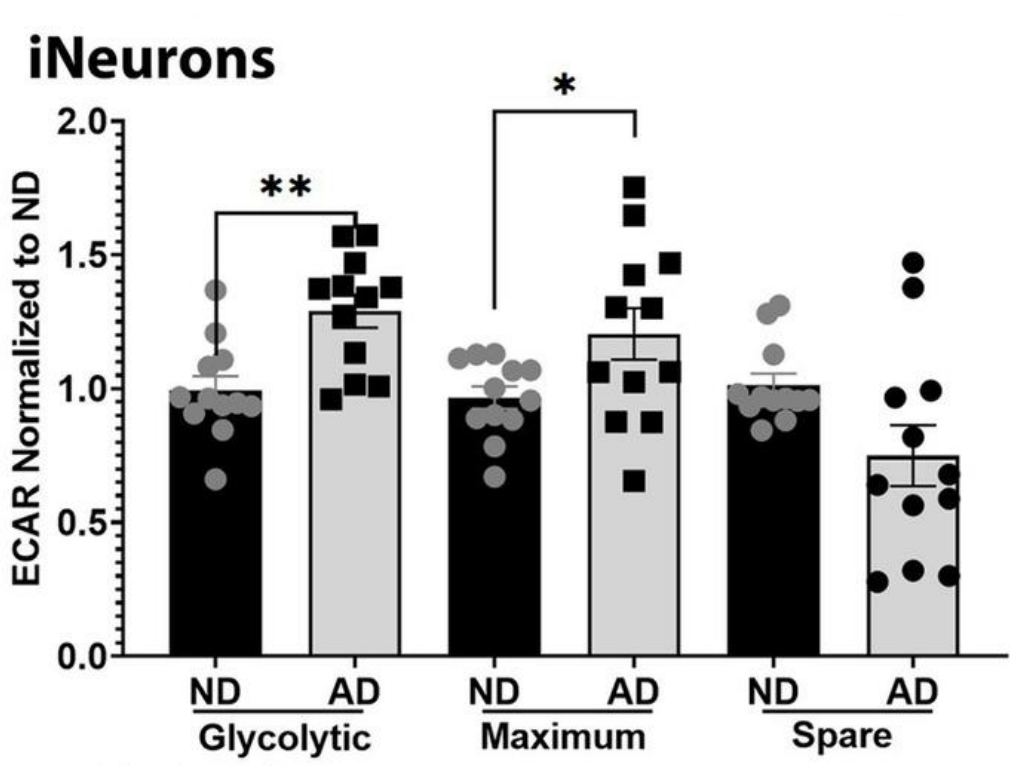


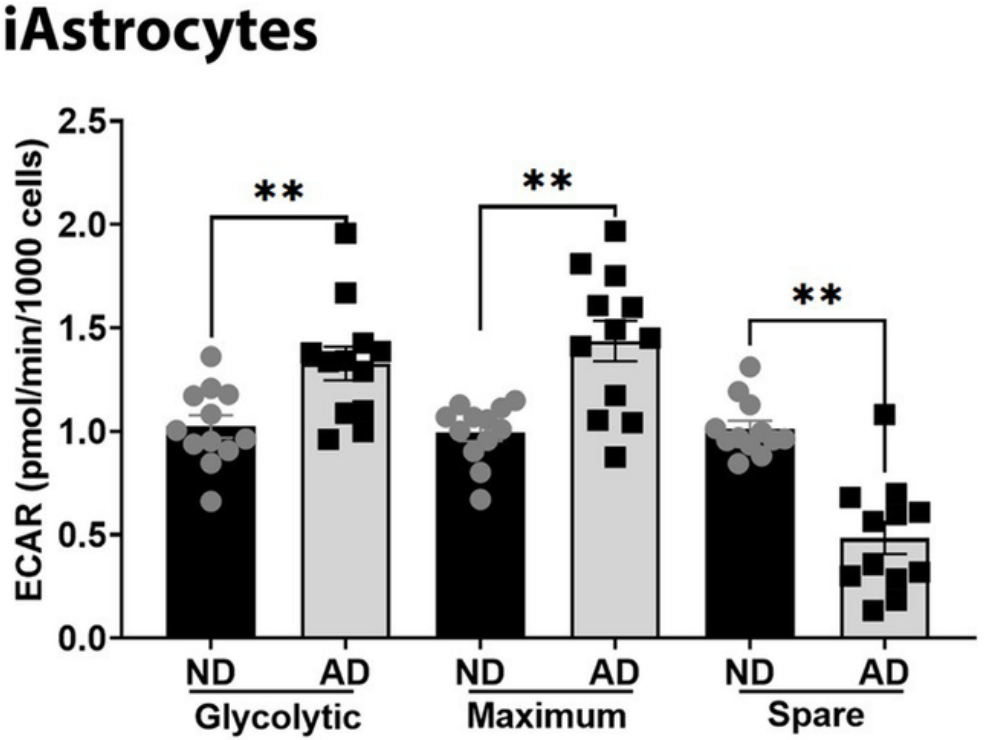






Neurons and Astrocytes Increase Glycolysis in AD





PMID: 37614699

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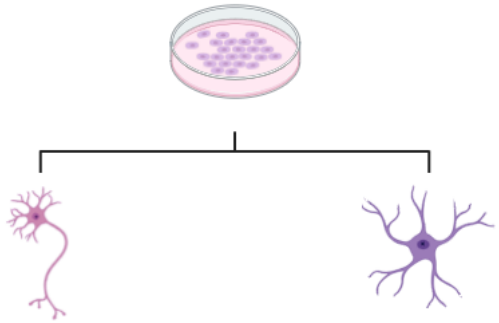
Can Modulating Mitochondrial Function Treat Alzheimer's Disease?

1

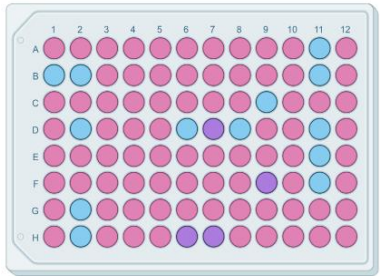
iPSCs from ND and AD patient donors
Sex as a biological variable

2



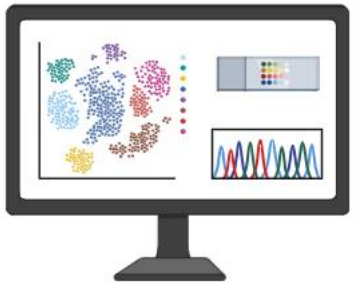
Patient-iPSC-derived neurons and astrocytes

3

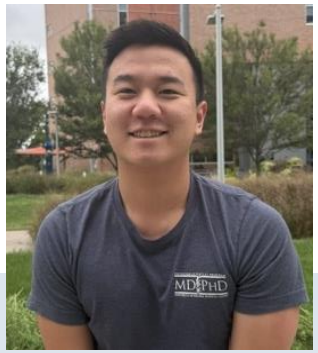


Targeted drug screen

4

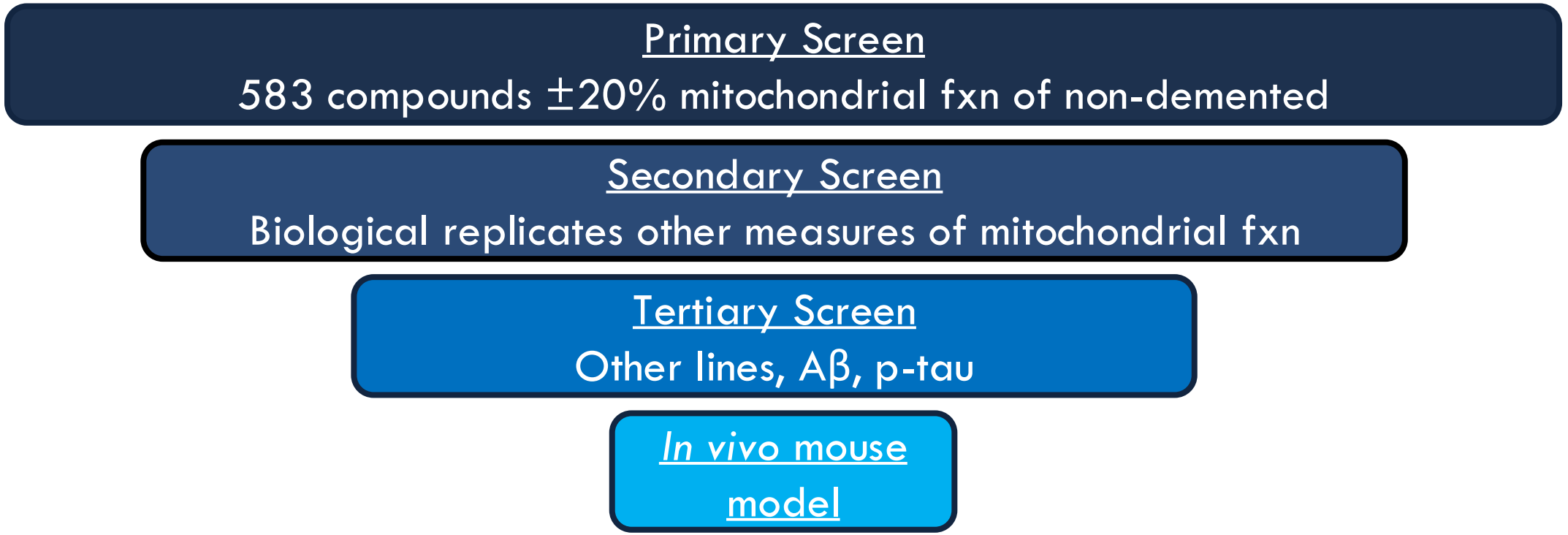


Phenotypic readout and mechanistic annotation

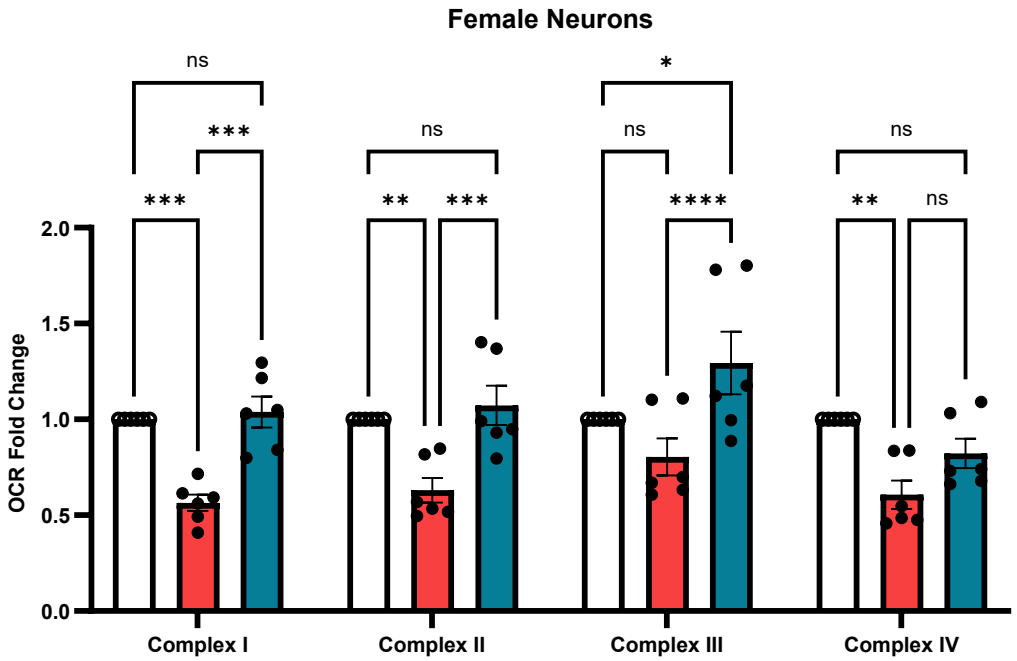


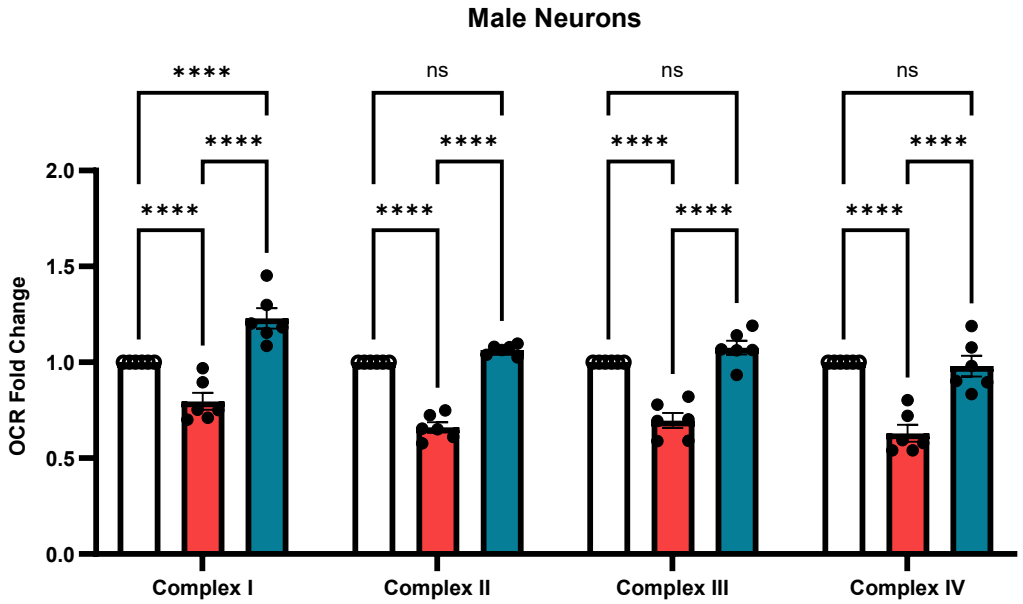
Daniel Chen, MD/PhD Candidate

Can Modulating Mitochondrial Function Treat Alzheimer's Disease?

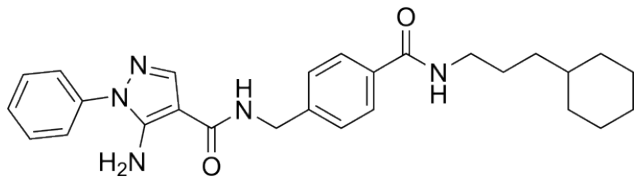


SR-318 is a protective hit in female and male neurons





ND
AD (-) SR-318
AD (+) SR-318



selective type-II inhibitor
targets p38α/β MAPK

Unpublished Data

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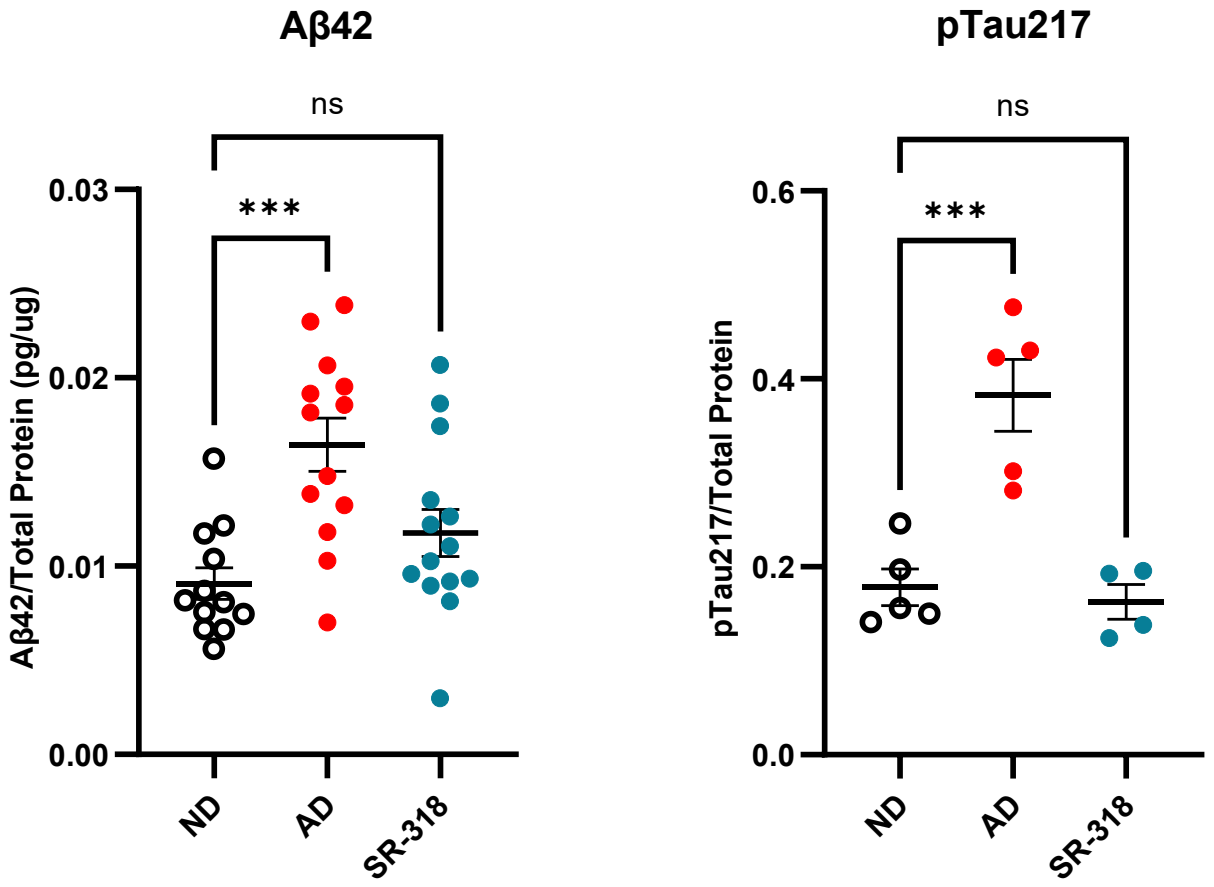
SR-318 normalizes amyloid and tau pathologies in neurons



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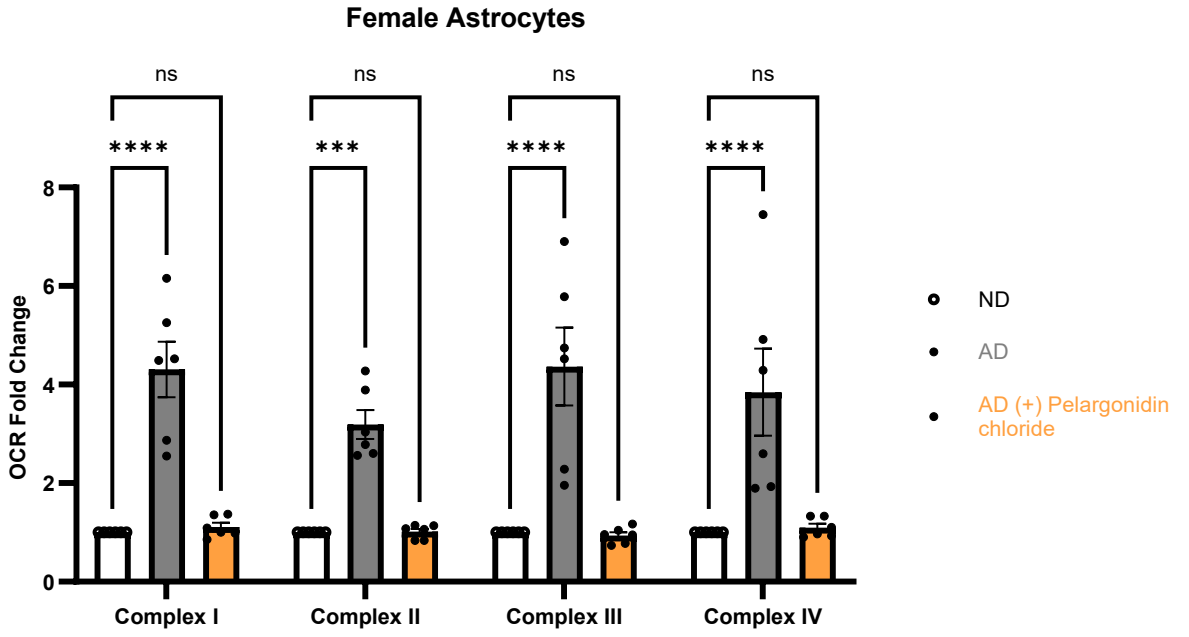
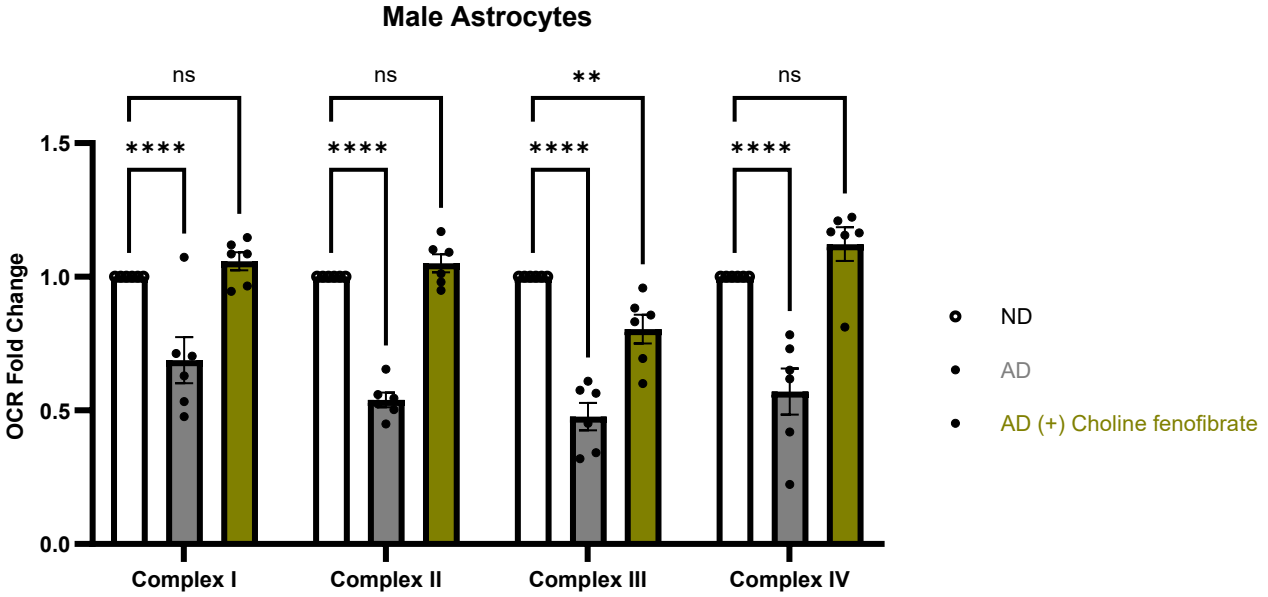
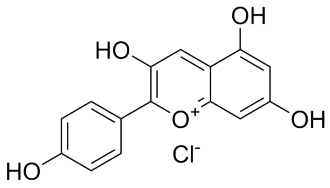
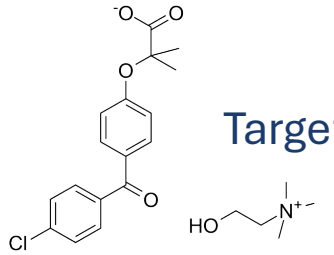
Sex-dependent protective hits in astrocytes







Pelargonidin chloride
Anthocyanidin (antioxidant)



Choline fenofibrate
Targets cholesterol metabolism

Unpublished Data

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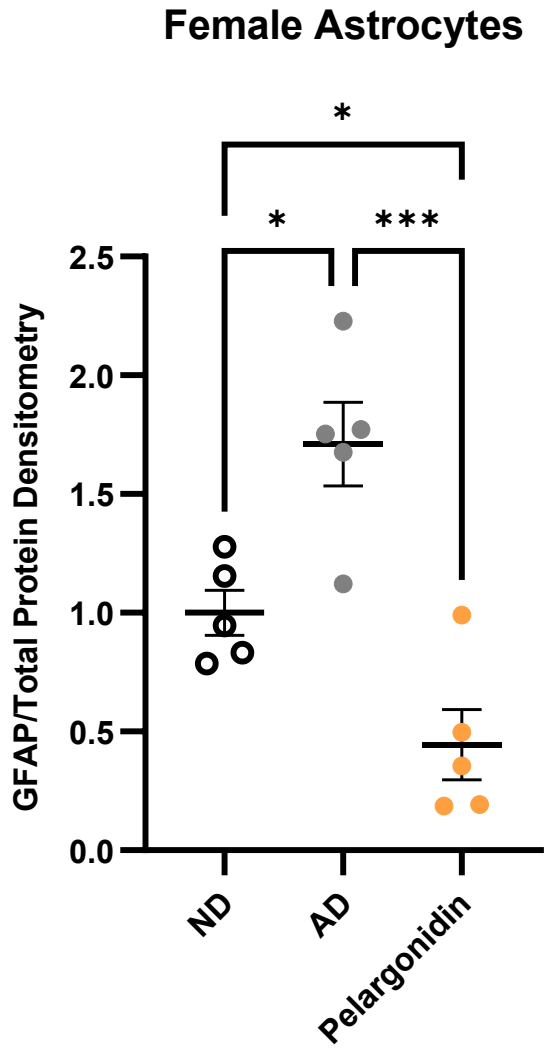

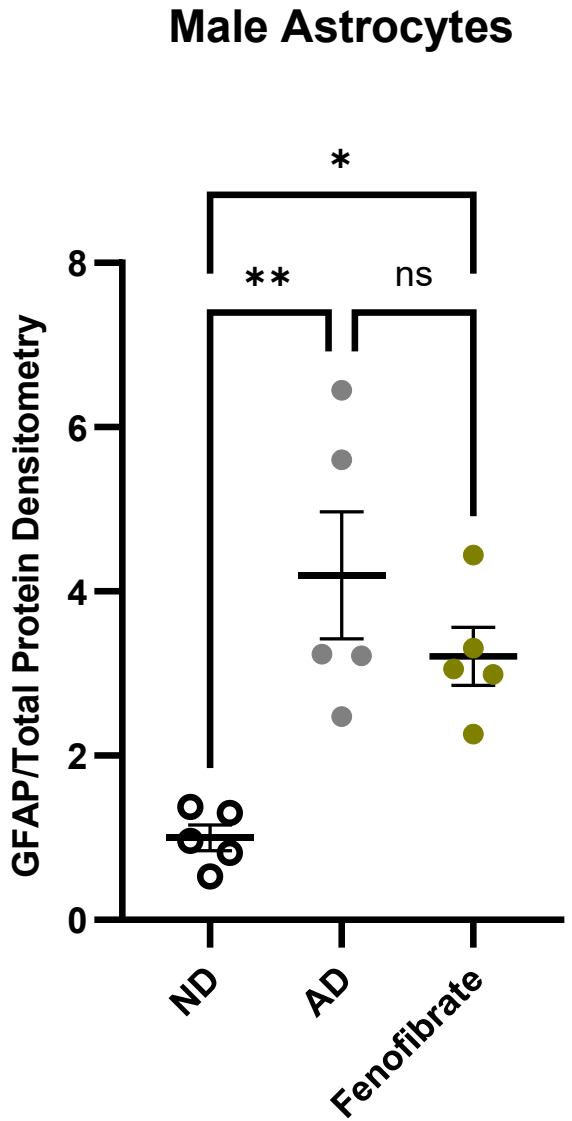

Unpublished Data

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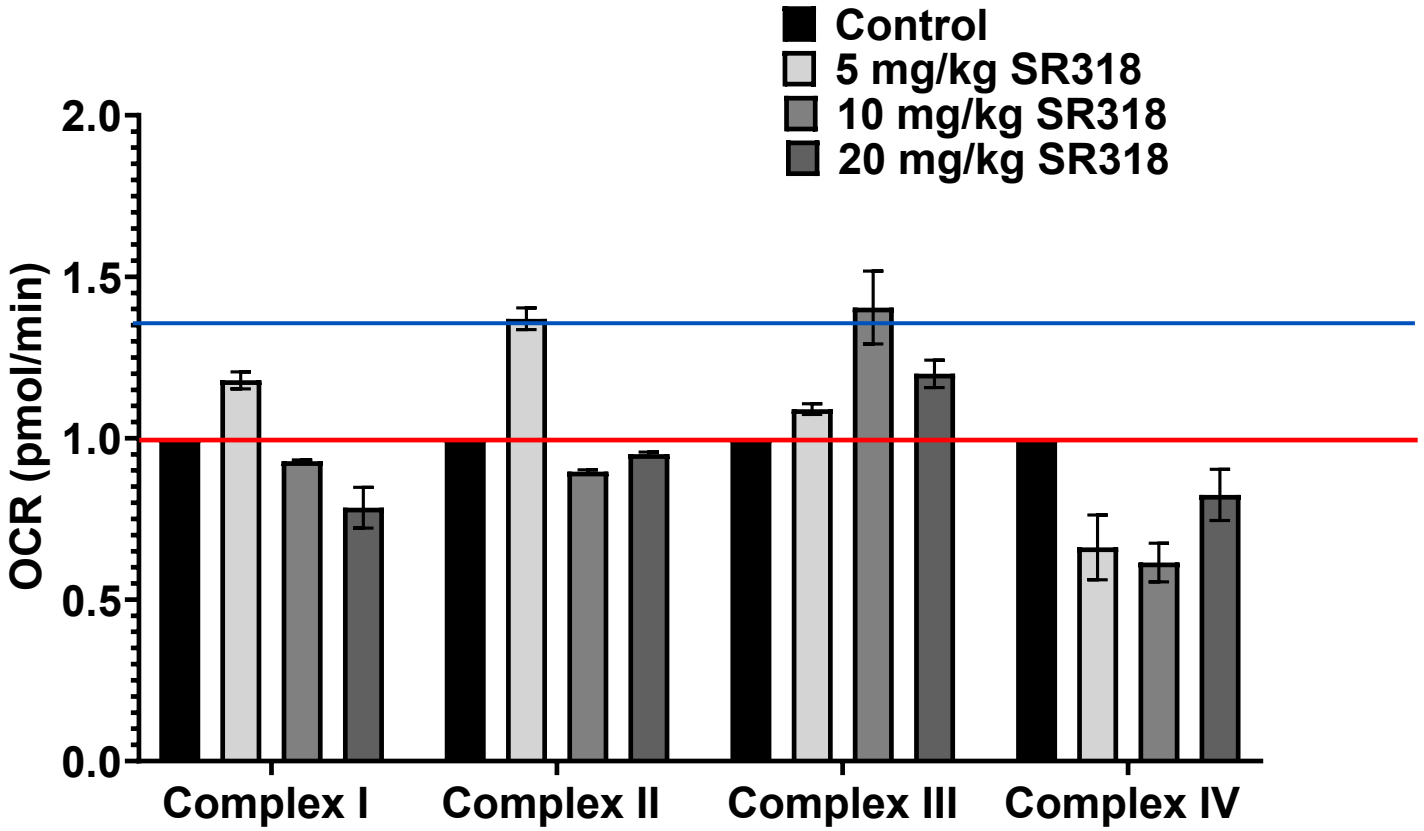
What are our next steps?

Moving into mice

- SR318 is safe in mice at a 5 mg/kg dose
- Will combine neuron and astrocyte hits to determine if additive



Brain mitochondria from healthy mice

Thank you!

Wilkins Lab Members:
Maggie Benson
Daniel Chen
Brittany Hauger
Keith Smith
Ashley Tetlow, PhD
Alexander Yang, PhD

Undergraduates: Julia Stopperan, Natalie Swerdlow

High school students: Caleb Gilmore, Abby Gongora, Layland Hamid, Anjali Priya, Trisha Rastogi, Nora Schumaker

Medical Students: Cole Birky, Laura Gonzalez Duran, Gracia Grabarić, Kaitlin Flannagan

Past Lab Members: Taylor Strope, PhD and Colton Lysaker, PhD, Vivien Csikos, PhD

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