Understanding the role of polyamines during tauopathies

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Tau Filaments

**Tau (microtubule stabilizing protein)**
- Misfolds & aggregates

- Associates >15 tauopathies with their own unique pattern of neurodegeneration and clinical manifestation

- Normally tau is in neuronal axons but mis-locates to dendrites and cell body.

- Tau can aggregate within neurons forming neurofibrillary tangles.

- Tangles are virtually indestructible. Leave “tombstone tangle” after neuron dies

- Tau mutations cause Pick’s disease, Progressive Supranuclear Palsy (frontal lobe dementia; distinct from AD)
Tau Directed Therapeutic Approaches

- Phosphatase (PP2A) activators
- Active and passive immunization
- HSP90 inhibitors
- Tau kinase inhibitors
- Tau reduction
- Dendritic tau (Fyn) blockers
- Tau assembly inhibitors
- Microtubule stabilizers
- Autophagy enhancers
- Antioxidant/ Mitochondrial strategies

Gotz et al 2011
What do polyamines do?

Polyamines do theses and much more...

- Increase protein clearance (Autophagy)
- Gene regulation
- Cell growth
- Neuronal stability
- Regulate neuronal activity
Polyamines decrease tau aggregation & promote microtubule assembly...but acetylated polyamines do not!!

**Tau Aggregation Assay**

**Microtubule Polymerization Assay**
SRM-Gene Therapy Increases Spatial Working Memory Recall

Polyamine Producing Gene Therapy

Radial Arm Water Maze
Using in vivo microdialysis to measure extracellular polyamines
Microdialysis Set Up
6” santopren tubing

Probe

Cap nut

Cannulae

Dr. Sandusky-Beltran & Team
Sampling During Diverse Behaviors

Resting

General Locomotion

A

Extracellular Acetylsperridine

Acetylsperridine (mg/mL)

Sample

100 mM KCl Infusion

nTg

P301S
Tau Aggregation-Polyamine Dysfunction Hypothesis

Critical Event
Take Homes

- Polyamines serve as small bioactive molecules that provide numerous functions for cells.

- Polyamines promote microtubule assembly—stabilize axons.

- Polyamines inhibit tau fibrillization—natural inhibitors of tau aggregation.

- Acetylated polyamines increase in models of tauopathy and fail to mimic polyamines—potential biomarkers.

- Modifying polyamines by gene therapy or drugs may improve memory impairment in tauopathy models—new therapeutic targets for tauopathies.

Polyamines… old molecules with new tricks!
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