Neuroinflammation-mediated Degradation of NMDA receptors and Tau Dephosphorylation Mechanisms Relating to Alzheimer’s Disease

Presented by Diane Youngstrom
Background: Alzheimer’s Disease

- Most common form of dementia
  - Progressive neurodegenerative disease
  - Incidence & prevalence increasing

- Pathology
  - Tau tangles (NFTs) & Aβ plaques
  - Synaptic & neuronal loss
  - Neuroinflammation (activation of microglia & astrocytes)

- No cure or disease-modifying drug
  - Many failed Phase 3 clinical trials (targeting Aβ)

- Memantine
  - 1 of 4 FDA approved drugs to mitigate symptoms (e.g. memory deficits)
    - Does not slow AD progression
  - NMDAR antagonist → blocks glutamate

Inhibiting phosphatases (PP1/PP2A) with okadaic acid blocks the tau dephosphorylation typically caused by CM.
NMDAR degradation not prevented by Phosphatase Inhibitors

NMDARs independent (or upstream) of the PP1/PP2A phosphatases that dephosphorylate tau under neuroinflammatory insult
Tau dephosphorylation may not be prevented by D-AP5

- Most (phospho)-tau roughly follow control/CM patterns → not significantly affected by D-AP5 or MTEP/JNJ
- Tau dephosphorylation by CM is independent of these glutamate receptors
D-AP5 prevents NMDAR Degradation

D-AP5 prevents NMDA receptors degradation by CM → NMDA receptor activation is required for NMDAR degradation by CM
Conclusion: Summary of Western blot Results

Control (untreated)

Okadaic acid + CM

D-AP5 + CM
Future Directions

• What is the mechanistic link between NMDAR and tau?
  o Fyn-mediated?
  o Is tau required for degradation of NMDA receptors?
    ▪ Tau knockout

• How does CM change neuronal network activity?
  o iGluSnFR live-cell imaging
  o Microelectrode array
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