Nitric Oxide Synthase Dysfunction Underlies Cerebrovascular Deficits in a Mouse Model of Tauopathy

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Introduction
Pathogenic soluble aggregated tau (tau oligomers) accumulate in the brain microvasculature of human patients with tauopathies, including Alzheimer’s disease1 (histological (top) and immunofluorescent (bottom) images at left), although the functional consequences of cerebrovascular tau accumulation are not yet understood. Therefore, the aim of the present study was to determine whether brain microvascular tau accumulation leads to microvascular dysfunction using in vivo and in vitro techniques.

 Neurovascular Uncoupling and nNOS Dysfunction in Tauopathy

Preliminary data suggests that exposure to oligomeric tau may not significantly inhibit nNOS phosphorylation in N2a neuroblastoma cells (f=4)=1.09, p=0.34. We are currently measuring nNOS activation in purified microvasculature of 8-month-old PS19 mice.

Methods
- Laser Doppler flowmetry was used to measure neurovascular coupling in male mice from the transgenic PS19 (P301S) mouse line. Wildtype littermates were used as controls.
- Cerebral blood flow in the somatosensory barrel cortex was measured with a Transonic laser Doppler probe. Neurovascular coupling was calculated as the percent increase in blood flow from baseline during contralateral electrical whisker stimulation. 10μM acetylcholine applied to the cortical surface was used to assess endothelium-dependent vasodilation.
- Mouse neuroblastoma N2a cells or human brain endothelial cells (HBEcs) were treated with tau oligomers or control media for 24h, lysed, and protein content was assessed.
- All statistical analyses were conducted using GraphPad Prism7. Statistical tests are described in the figure legends.

Conclusions
- Tauopathy is associated with cerebrovascular dysfunction
- Inhibition of NOS phosphorylation by pathogenic soluble tau aggregates may underlie brain vascular dysfunction
- Therapeutic modulation of pathogenic tau may mitigate brain microvascular deficits, which occur prior to clinical onset in Alzheimer’s disease2 and potentially other tauopathies

References
1. Castillo-Caranza et al., 2017, Aging and Disease
2. Lourenço et al., 2014 Free Radical Biology and Medicine
3. Iturria-Medina et al., 2016, Nature Communications

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