Specialty Area: Translational Pathways & Validation

Speaker Name: Robia G. Pautler, Ph.D.

Highlights:

- Using MEMRI to monitor transport deficits in a progressive tau mouse model
- Incorporating molecular methods to define/understand MEMRI data
- Incorporating immunohistochemistry to define/understand MEMRI data

Talk Title: "Molecular Biology Has Your Back — Validating MEMRI transport data"

Target Audience: Preclinical imagers interested in translational validation of their MRI datasets.

Outcome/Objectives:

- Attendees will be able to understand the principles behind specific molecular biology and immunohistochemistry methods to validate MRI datasets.
- Attendees will be able to incorporate some of these strategies into their own research programs.

Purpose: The purpose of this presentation is to demonstrate the process by which molecular biology and histology can be used to validate and better understand preclinical MRI imaging data.

Methods:

- Manganese Enhanced MRI (MEMRI) to measure axonal transport in the murine olfactory system will be described.
- Immunohistochemistry general methodologies as well as the specific methodologies pertinent to this study will be described.
- Molecular Biology methodologies, specifically Western blots will be described. The general principals as well as the specific methodologies will be described.

Results:

Axonal transport is vital for neurons and deficits in this process have been previously reported in a few mouse models of Alzheimer's disease prior to the appearance of plaques and tangles. However, it remains to be determined whether axonal transport is defective prior to the onset of neurodegeneration. The rTg4510 mouse, a Fronto-temporal Dementia and Parkinsonism-17 (FTDP-17) tauopathy model,over-express tau-P301Lmutation found in familial forms of FTDP-17, in the forebrain driven by the calcium-calmodulin kinase II promoter. This mouse model exhibits tau pathology, neurodegeneration in the forebrain, and associated behavioral deficits beginning at 4-5 months of age. Using the MEMRI technique on 1.5, 3, 5, and 10-month old rTg4510 mice and littermate controls, we found significant axonal transport deficits present in the rTg4510 mice beginning at 3 months of age in an age-dependent manner. Using linear regression analysis, we measured rates of axonal transport at 1.5, 3, 5, and 10 months of age in rTg4510 and WT mice. Axonal transport rates were observed in rTg4510 mice at 48% of WT levels at 3 months, 40% of WT levels at 5 months, and 30% of WT levels at 10 months of age. In order to determine the point at which tau appears in the cortex, we probed for phosphorylated tau levels, and found that

pSer262 is present at 3 months of age, not earlier at 1.5 months of age, but observed no pathological tau species until 6 months of age, months after the onset of the transport deficits. In addition, we saw localization of tau in the ONL at 6 months of age.

Conclusion: In our study, we identified the presence of age-dependent axonal transport deficits beginning at 3 months of age in rTg4510 mice. We correlated these deficits at 3 months to the presence of hyperphosphorylated tau in the brain and the presence within the olfactory epithelium. We observed tau pathology not only in the soma of these neurons but also within the axons and processes of these neurons. Our characterization of axonal transport in this tauopathy model provides a functional time point that can be used for future therapeutic interventions.

In conclusion of this presentation, attendees will be presented with a research problem, how our lab addressed this question with the methodology, MEMRI, and then validated the results with histological and molecular biology methods. Emphasis will be placed on the necessity for these validation markers.

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