^{31}P NMR of the P301L Mouse Model of Frontotemporal Dementia and AD

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Introduction

The focus of this study was to investigate whether *in vivo* expression of P301L tau protein in the mouse alters the cerebral phospholipid profile specific to AD-related pathology. This hyper-phosphorylated form of tau is involved in white matter degeneration, microtubule destabilization and disruption of the myelinating functions of oligodendrocytes. The *in vitro* ^{31}P NMR spectroscopy of Alzheimer's disease (AD) tissue has historically shown changes in phosphomonoester (PME) and phosphodiester (PDE) ratios (1) that appear to be common to a number of disease states. The use of 2D NMR to identify individual esters may eventually provide a causal link between tau overexpression in forebrain structures and altered phospholipid profiles in mouse models of cognitive decline.

Experimental

Mouse brains were snap-frozen in liquid nitrogen and homogenized in D_2O for *in vitro* spectroscopy. A ^{31}P one-pulse experiment was collected using a 5mm probe on the 14 T system in the AMRIS facility. Two-dimensional ^{1}H {^{31}P} HMBC experiments were used to separate and identify the PMEs and PDEs (2). The *in vivo* ^{31}P spectra were acquired on the 17.6 T system in the AMRIS facility using a 6-mm x 9-mm surface coil (Doty Scientific) centered over the frontal cortex of the mouse.

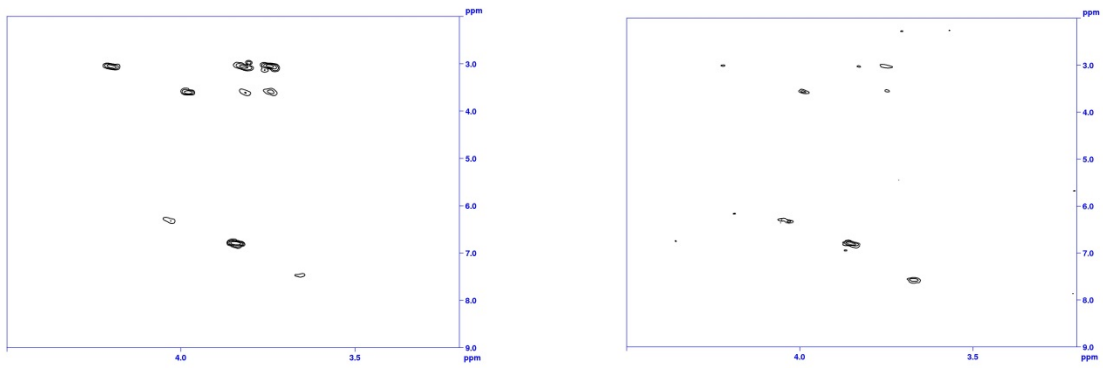

Fig. 1. 14T ^{1}H{^{31}P} HMBC 2D spectra of homogenates of a control mouse brain at left and a P301L mouse brain at right.

Results and Discussion

The two-dimensional ^{1}H {^{31}P} HMBC experiments at 14 T shown in Fig. 1 reflect an altered PME to PDE ratio in the P301L mouse. Spiking experiments with standard lipids will be used to confirm the identity of specific esters and establish the phospholipid profiles. The 1D spectra collected *in vivo* at 17.6 T can define the ratio of PMEs to PDEs but are not able to characterize specific lipids. Future *in vivo* work will use ^{31}P chemical shift imaging to better localize and quantitate the metabolites. The goal is to understand the role of ceramides and other membrane raft components in AD-related pathology.

Acknowledgements

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References

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