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EFFECTS OF ENDOGENOUS AND HUMAN 4R TO 3R TAU SPLICING

Smruti Rath

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Tau protein deposition has been implicated in the progression of several diseases collectively referred to as Tauopathies. This study investigated the effects of reducing 4R Tau *in vivo* to understand the mechanisms by which Tau neurofibrillary tangles affect the progression of disease. In order to do so, antisense oligonucleotides (ASOs) were utilized for the purpose of 4R to 3R Tau splicing in mice expressing either mouse (mTau) or human tau (hTau). These ASOs are short nucleotide sequences that were designed with a modified backbone to bind to Tau mRNA and alter its splicing.

Three cohorts of hTau mice were tested for decreased disease pathology. Treatment groups were saline, scrambled oligonucleotide, and 4R to 3R splicing oligonucleotide. Mice received the drug for 28 days (25 µg/day) via an osmotic pump to the right lateral ventricle. Following drug treatment, mice were injected with PTZ (Pentylenetetrazole) to induce seizures which were observed and scored. The mice were then euthanized for brain tissue collection and Tau protein levels were measured by quantitative real-time PCR. A cohort of mTau mice was also treated to observe location of Fyn and Tau protein isoforms in the synaptosome using Western Blot techniques.

The splicing oligonucleotides successfully reduced 4R Tau levels, and the scrambled oligonucleotide from the second cohort of hTau mice maintained similar levels of Total Tau. Current results indicate that 4R to 3R splicing in hTau mice did not significantly reduce Tau pathology. Results also did not indicate a significant decrease in Fyn protein levels in the Synaptosome following splicing treatment. Future directions include using more cohorts of hTau mice to test for decreased seizure pathology with 4R to 3R splicing. Co-immunoprecipitation will also be carried out to determine binding of Fyn to 4R and 3R Tau in the Synaptosome of mTau mice.