Characterization of Tau Expressing P301S Mouse Model for Tauopathy – Longitudinal Brain Structural and Metabolic Profile

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INTRODUCTION & STUDY DESIGN

Background: P301S (B6.C3-Tg(TgP301S)4580Nak/J) mouse is a widely used tauopathy model. Majority of the work described in the model focuses on the brain pathology after 6 months of age, when there has been reported more prominent tau pathology, neuronal cell loss and atrophy. As the early development of tauopathy, behavioral phenotype and both structural and metabolic profile of the brain in P301S (Tg) model have not been well characterized, we sought to examine longitudinal phenotype of this model with MR anatomical imaging, 1H-spectroscopy, metabolic imaging (PET) and behavioral features, and comparing them to aged matched background strain mice.

METHODS

Animals Female (n=20) and male (n=19) P301S (B6.C3-Tg(TgP301S)4580Nak/J, Jackson Laboratory, USA) and age matched BIOCHIP back ground strain mice (n=20 for both genders) at the age of 7 weeks were enrolled to the follow-up study. Mice were kept in standard housing conditions on ad libitum food and water.

MR experiments: Imaging was performed at Bruker Biospec UPR 41W 11.7T magnet (Bruker Biospin GmbH, Ettlingen, Germany) in software anesthetized animals.

Structural T2-MRI & HM-MR Spectroscopy: A Turbo-RARE with in-plane resolution of 78 microns and thirty-one 0.45 mm slices. Bilateral hippocampal voxel (2.24x3.15 mm, 7.2 µl volume) with PRESS sequence (TE/TR = 10/200 ms). Data as averaged 912 excitations, number of points 2048 and spectral width of 5 kHz. Peak areas for resolved metabolites were analyzed using LCModel (Stephen Provencher Inc., Oakville, Canada).

*FDG PET: At the age of 17 months, male mice were placed overnight prior to PET imaging to stabilize blood glucose levels. 

At-test mice (n=1) showed significant differences with age, and PET mice (n=10) and 4 g were dosed with ca. 15 MBq of 18FDG i.v. Static 30 min PET scan (500 – 700 kvi) was started 30 min post FDG dosing followed by a CT scan (BioPET/CT, Siemens). The experiments were repositioned with 3D OSEM with attenuation correction and image analysis was performed with PMOD software (V3.7, PMOD Technologies).

Open field: The open field test is performed during the mouse light cycle and under a normal lighting in the sound attenuated rodents that is divided evenly on to the test cages. The test device (square 27x27x20.3 cm) is constructed of Plexiglas. The paths of the mice were recorded by activity monitor (Med Associates Inc.) for 30 min.

Fear conditioning: Mice were brought to the experimental room for at least 30 min acclimation in the experimental room conditions prior to testing. The contextual fear conditioning test is modified from Comery et al. (2000) (Comery TA et al., Acute gamma-secretase inhibition improves contextual fear conditioning in the Tg2576 mouse model of Alzheimer's disease. J. Neurosci. 2005 Sep 28;25(39):8989-9002). The training and testing were conducted on two consecutive days, using a Coulbourn Freezeframe system (Coulbourn, Whiptail PA, USA).

Radial arm water maze: Mice are brought to the experimental room for at least 30 min acclimation to the experimental room conditions prior to testing. Two day radial arm water maze has been described in detail previously (Almeida et al., 2004). Briefly, a six arm maze is subtended in a pool of water; and a platform is placed at the end of one arm. The mice receives 15 trials per day for 2 and on each trial is started in a different arm while the arm containing the platform remains the same for each mouse. Using visual cues around the room, the mice learns the position of the escape platform. The first 10 trials are considered training and alternate between a visible and a hidden platform. The final trials for day 1 and all trials on day 2 use a hidden platform. The number of errors (incorrect arm entries) are counted over a 1 min period. The errors are averaged over three trials results in 10 blocks for the 2d period.

RESULTS

**Figure 1.** Example images from T301S mouse aged matched control mice at 2 months of age (A). T2 magnetic resonance imaging of whole brain (B). T2 magnetic resonance imaging of whole brain (C). T2 magnetic resonance imaging of whole brain (D). T2 magnetic resonance imaging of whole brain (E).

**Figure 2.** Example FDG PET imaging data from T301S (A) and age matched control mice (B) at 7 months of age (A). PET imaging data from T301S and age matched control mice (B). T2-magnetic resonance imaging of whole brain (C).

**Figure 3.** Open field spontaneous locomotor activity at 8 weeks (2 mo) and 24 weeks (8 mo) between T301S and age matched control strain mice. No significant difference in overall motor activity assay were seen. Data presented as mean ± SEM, n=4-5 males and only female genotypes. Same mice were followed for whole monitoring period. No significant gender differences were observed (data not shown).

**Figure 4.** Fear conditioning response in T301S mice between T301S and age matched control strain mice. Clearly reduced freezing activity in T301S mice compared to control mice at 10 months of age, *p<0.01. Data presented as mean ± SEM, n=9-10/ gender/genotype.

**Figure 5.** Radial arm water maze (RAWM) performance in T301S mice was found to be clearly impaired when compared to age matched control strain mice as seen on increased latency to find the platform or increased number of errors, **p<0.01. Data presented as mean ± SEM, n=19-23/gender/genotype. No differences between genders were observed.

CONCLUSIONS

In this study we looked at known tau expression mouse model longitudinally for possible changes and differences over time when compared to control strain mice. We specifically looked at brain anatomical and metabolic differences and temporal changes during aging and found:

1. *1H-MRS and T2-MRI showed significant differences between P301S and control strain mice, especially at early time-points, but later found these differences to level off. Metabolic differences were found to be present in both genders (data not shown) with some differences in metabolites with significant differences. Previous reports atrophy in the P301S mice between 6 months of age to 11 months were not confirmed in this study, although control strain whole brain and striatal volumes were found slightly but significantly larger than P301S mice.

2. *FDG consumption was found to be significantly higher in multiple brain structures in P301S when compared to control mice

3. *Open field spontaneous locomotor activity was not found to be different between P301S and control strain mice at 2 or 6 months of age.

4. Fear conditioning responses and radial arm water maze performance were found significantly different between P301S mice compared to control strain mice. Ongoing tau analysis in the brain tissues is ongoing to evaluate key protein expression levels in this known mouse model for tau expression and cognitive deficits. Different options for using aged matched littermate mice as controls are currently being investigated.