Characterizing longitudinal biochemical alterations in Alzheimer's disease: A neuroimaging study in the TgF344-AD rodent model

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, presenting neuropathologically with amyloid beta (Aβ) plaques and hyperphosphorylated tau tangles, clinically accompanied by progressively declining memory and cognitive functions[1]. Although reasonably characterized, a means for definitive diagnosis antemortem and effective treatment is non-existent. Experimentation in animal models presents a promising avenue for the development of translational biomarkers and testing of candidate therapeutics. Interpreting therapeutic finding in animal models primarily requires discerning pathological features of the model from control cohorts and eventually treated transgenics. **Here, we report preliminary results from a neuroimaging study using magnetic resonance spectroscopy (MRS) to characterize the longitudinal neurochemical alterations evident in the TgF344-AD rat model**. This is a highly translatable model that age-dependently accumulates Aβ and tau pathology, in addition to synaptic dysfunction and neuronal loss[2]. Neurochemical changes are compared longitudinally to behavioural alterations using the Barnes maze, a measure of spatial reference memory and learning[3]. Additionally, sex-dependent differences will be considered, as are evident in human AD[4].

Methods

^{1}H MRS acquisition and analysis: Localized MRS data were acquired on a 7 Tesla Bruker Biospec 70/30 Scanner from a 31 μL voxel (2.5x3.5x3.5) mm in the dorsal hippocampus. FASTMAP was used for shimming (water linewidth range 7.8-14.7 Hz) prior to PRESS MRS acquisition (TR/TE=3000/11 ms). Pre-processing was performed using the FID-A toolkit; MRS spectra were analysed in LCModel with metabolites referenced to total creatine[5,6]. **Barnes Maze:** Training: Rats are given a maximum of 3 minutes to use spatial cues surrounding the maze to find and enter an escape box, located under one of 20 identical holes around the perimeter of the maze. Probe: 48 hours after the last training trial, the escape box is removed and rats are given the entire 3 minutes to search the maze[7].

Results

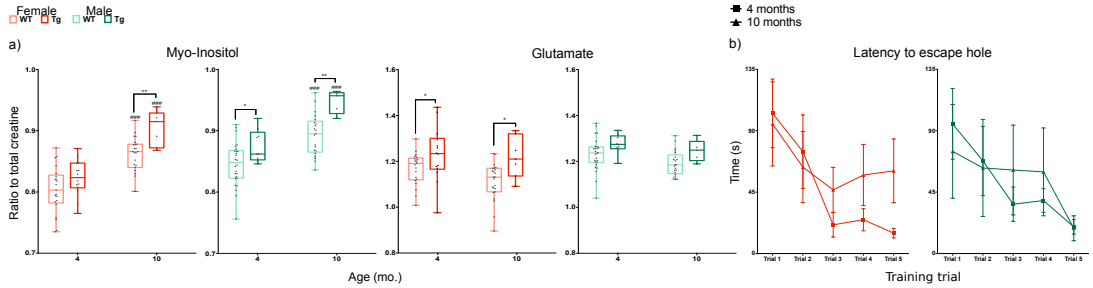
Results at 4 and 10 months indicate elevated myo-Inositol (mI) in transgenic rats relative to wild-type, and in males relative to females. Genotype- and sex-dependent increases in glutamate (Glu) levels are also evident (Fig.1a). Barnes maze analysis indicates impaired location recall in transgenics, across sexes, at 10 months compared to transgenics at 4 months (Fig. 1b).

Discussion

1H MRS allows for quantification of numerous brain metabolites that can indicate specific aspects of pathology. For example increases in mI reflect early inflammatory processes, which are also observed in human AD[8]. Additionally, elevated Glu in female transgenics may suggest early excitotoxicity[9]. Decreased latency across trials in 4 month, but not 10 month transgenics is suggestive of age-related cognitive impairments, such as spatial memory deficits[4]. Overall, this work provides a means of characterizing the TgF344 rat model of AD, and deciphering sex differences.

Conclusion

Early findings in this longitudinal study are indicative of the value of MRS in pinpointing disease-related differences in a rat model of AD. The combination of MRS with behavioural data allows for understanding the relationships between metabolite alterations and cognitive changes. Additional longitudinal analysis will further explain the validity of the TgF344-AD model in representing AD.



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