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In vivo 1H MRS study of a mouse model for fragile-X-associated tremor/ataxia syndrome at 14.1 T

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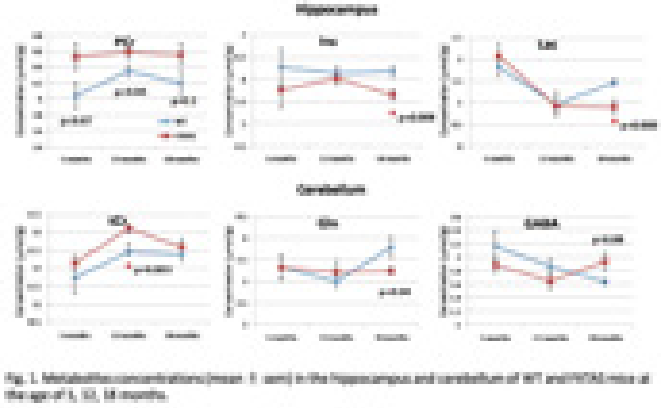
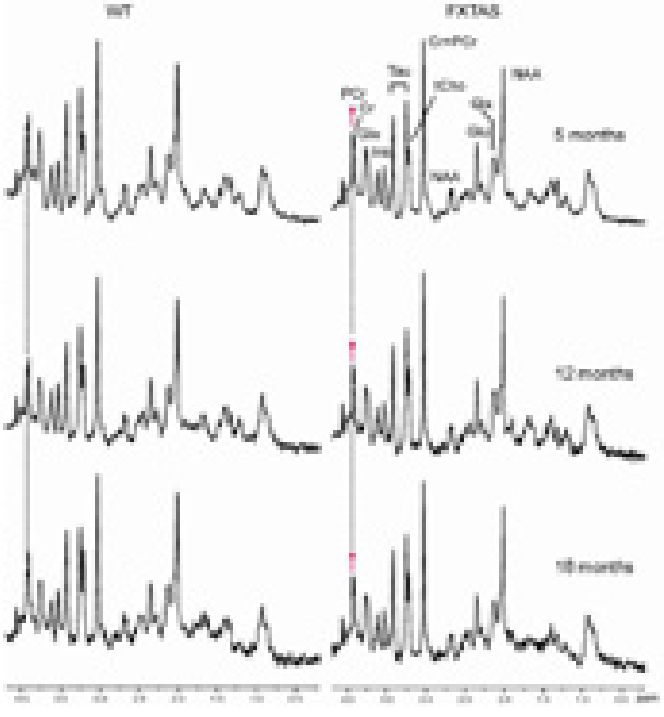
Introduction: Fragile X-associated Tremor/Ataxia Syndrome (FXTAS) is a recently identified neurodegenerative disorder caused by the expansions of CGG repeats (55-200 CGG) in the non-coding region of the Fragile X mental retardation 1 gene [1]. A knock-in mouse model with a $(CGG)_{98}$ repeat in the permutation range has been generated and used as a model for FXTAS [1]. In this mouse model, intranuclear inclusions characteristics of FXTAS were detected in neurons and astrocytes in the cortex, brainstem and with the highest density in hippocampus. Despite the presence of intranuclear inclusions and the description of a mild phenotype, no brain lesion or structural abnormality has been described. The aim of this study is to investigate the longitudinal changes in neurochemical profile of the FXTAS knock-in mice in vivo using ^{1}H MRS.

Subjects and Methods: Male FXTAS knock-in mice (C57BL/6J background, n = 7) [1] and male WT littermates (n = 7) were anesthetized with 1.5-2% isoflurane during MRS measurement. *In vivo* MRS experiments were performed on a 14.1T/26cm magnet (Agilent/Magnex). Short-TE MRS sequence, SPECIAL[2] (TE = 2.8ms, TR = 4s) was used to measure ^{1}H NMR spectra in hippocampus and cerebellum at the age of 5 months, 12 months and 18 months. Metabolite concentrations were quantified by LCModel [3] using water as a reference.

Results and Discussion: At the age of 5 months (no behavioral alterations [1]), metabolites concentrations measured in hippocampus and cerebellum of FXTAS knock-in mice show similar pattern as those of WT mice (not shown). However, an increased trend of PCr was observed in both cerebellum (p=0.086) and hippocampus (p=0.07) (Fig. 1), which was also noticed in the in vivo spectra and continued in hippocampus at the age of 12 and 18 months (Fig. 2). Furthermore, at the age of 18 months, compared to WT mice, the FXTAS mice displayed a decrease of myo-inositol (-9%, p=0.008) and lactate (-39%, p =0.008) in hippocampus, an increase of GABA (+18%, p=0.08) and a decrease of glutamine (-15%, p=0.04) in cerebellum (Fig. 1). We conclude that there are merely weak changes in metabolites concentrations between the FXTAS mice and WT mice. The elevated trend of PCr in hippocampus might be an early indication of FXTAS prior to the formation of inclusions, which should be further validated by ^{31}P spectroscopy.





References:

[1] Van Dam et al., Behavioural Brain Research. 162 (2005)
[2] Mlynárik et al. MRM 56 (2006)
[3] Provencher, MRM. 30 (1993)