Assessment of Neurodegeneration Reversal in a Spinocerebellar Ataxia Type 1 (SCA1) Mouse Model by ^{1}H MRS at 9.4 Tesla

G. Oz[1], H. B. Clark[1], C. D. Nelson[1], D. M. Koski[1], M. L. Vollmers[1], and H. T. Orr[1]

[1]University of Minnesota, Minneapolis, MN, United States

Introduction

Spinocerebellar ataxia type 1 (SCA1) is a hereditary, polyglutamine-induced neurodegenerative disorder that results in loss of motor coordination primarily caused by cerebellar Purkinje cell dysfunction and loss (1). Recently a conditional transgenic SCA1 mouse model was developed where the expression of the mutant human ataxin-1 protein was put under doxycycline regulation such that its expression could be turned on and off at will (1). This model demonstrated that the neurological phenotype is reversible at early- to mid-stages of disease (1). We utilized this model to assess the sensitivity of MRS biomarkers to disease reversal, which we also assessed by histology following doxycycline treatment.

Methods and Subjects

Conditional SCA1 mice and wild type controls (background strain FVB) were scanned at 9.4 tesla under 1.5 - 2% isoflurane anesthesia at ages 6, 12 and 24 weeks with a quadrature surface coil. Half of the SCA1 mice were treated with doxycycline from 12 to 24 weeks (mid-stage disease at 12 weeks). Spectra from the cerebellum (5 - 7 µL volumes) were acquired with a short echo (TE = 15 ms) localization by adiabatic selective refocusing (LASER) sequence (2). Metabolites were quantified with LCModel (3) using unsuppressed water as reference. The LCModel basis set was generated with MATLAB software by simulating the spectral pattern of each metabolite using density matrix simulations (4). Only results with Cramér-Rao lower bounds (CRLB) $\leq$ 50% were included in the analysis. Metabolites quantified with CRLB $\leq$ 50% in at least half of the spectra were included in the neurochemical profile. Data from the different mouse groups were compared using the two-tailed, unpaired student's t-test. Histology was performed on paraffin-embedded sections using hematoxylin-and-eosin and Luxol-fast-blue-PAS.

Results and Discussion

High spectral quality enabled reliable quantification of 17 metabolites in the mouse cerebellum (Figs. 1, 2). Multiple MRS biomarkers were identified: NAA, taurine and *myo*-inositol were significantly different in the conditional, untreated SCA1 mice relative to controls at all ages, while aspartate, GABA and total creatine were abnormal only at 24 weeks (Figs. 2, 3). Stopping the mutant ataxin-1 expression with doxycycline at 12 weeks partially reversed these changes (Figs. 2, 3). Some statistical differences that the untreated animals displayed at 24 weeks relative to controls were not present in the treatment group, while others were reduced in significance level (Fig. 2). Differences between the treated and untreated groups were apparent in spectra from individual animals, e.g. note the changed peak ratios of taurine-to-choline and *myo*-inositol-to-taurine in the treated animal (Fig.1). The partial reversal of neurochemical changes was in agreement with pathological findings. This was also in excellent agreement with the partial recovery of Purkinje cell pathology and motor dysfunction reported in these mice when the doxycyline treatment was initiated at mid-stages of disease (1). These data demonstrate the ability of MRS to non-invasively detect reversal of neurodegeneration and its potential utility in future pre-clinical and clinical trials.

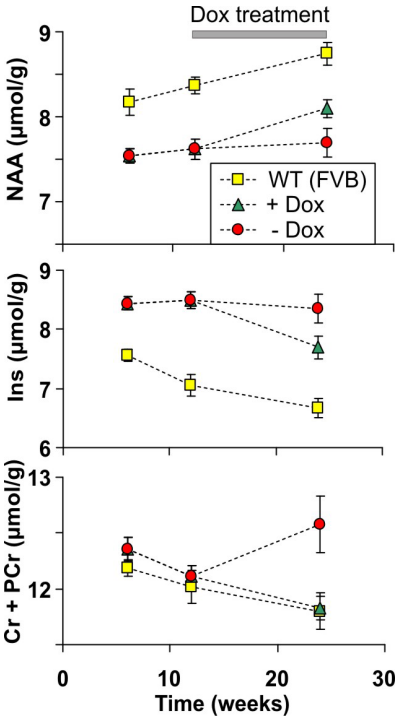

Fig. 3. Progression of alterations in select metabolites in SCA1 mice with and without doxycycline treatment. Error bars represent SEM.

References: **1.** Zu et al, *J Neurosci*, 24: 8853, 2004. **2.** Garwood and DelaBarre, *J Magn Reson*, 153: 155, 2001. **3.** Provencher SW, *MRM*, 30: 672, 1993. **4.** Henry et al, *MRM*, 55: 250, 2006.

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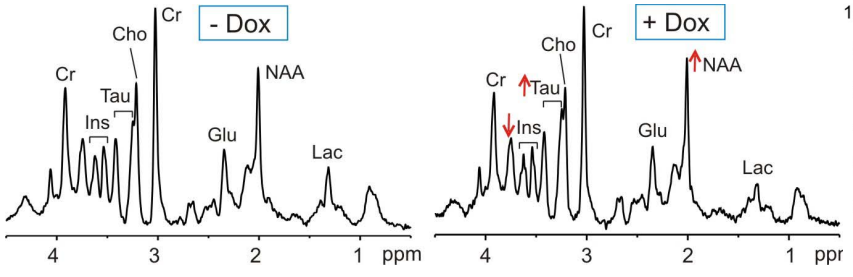

Fig. 1. ^{1}H MRS spectra from one treated (+ Dox) and one untreated (- Dox) conditional SCA1 mouse at 24 weeks. Cr: creatine; Cho: choline; Tau: taurine; Glu: glutamate; NAA: N-acetylaspartate; Ins: *myo*-inositol, Lac: lactate. The changes in NAA, Ins and Tau with treatment are marked with arrows.

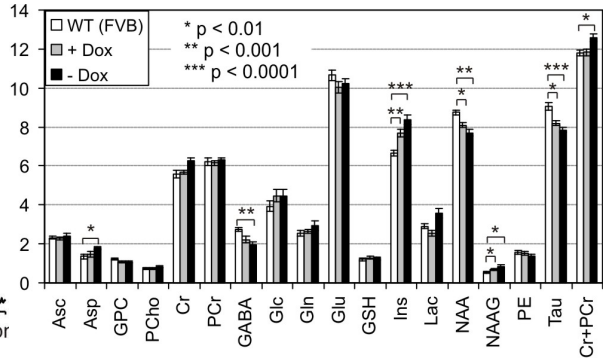

Fig. 2. Average (± SEM) metabolite concentrations (µmol/g) at 24 weeks in treated (+ Dox) and untreated (- Dox) SCA1 mice and wild type controls (N = 9 in each group). Only those changes are shown where $p < 0.01$ due to multiple comparisons.