Regional metabolic abnormalities as a function of age in familial amyotrophic lateral sclerosis (FALS) mice assessed using 1H magnetic resonance spectroscopy (1H MRS).

J-K. Choi[1], A. Dedeoglu[2], and B. G. Jenkins[3]

[1]Radiology, MGH-NMR Center and Matinos Center for Biomedical Imaging, Charlestown, MA, United States, [2]VA Medical Center, Bedford, MA, United States, [3]MGH-NMR Center and Martinos Center for Biomedical Imaging

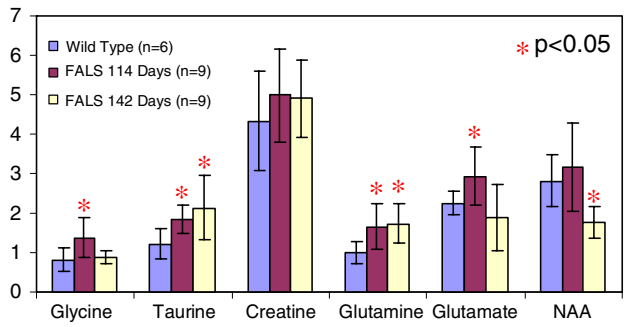
Introduction Amyotrophic lateral sclerosis is characterized by motor neuron loss, rapidly progressive motor weakness and early death. We wished to characterize the regional and temporal progression of metabolic abnormalities in FALS mice using *in vivo* and *in vitro* ^{1}H magnetic resonance spectroscopy (MRS).

Method Male transgenic mice carrying a Cu^{2+}/Zn^{2+} superoxide dismutase 1 (SOD1) [B6SJL-TgN(SOD1-G93A)1] were bred with female B6SJL mice. The offspring were genotyped and divided into transgenic (TG) and wild-type (WT) animals. At selected time points between 84-142 days of age, mice were decapitated into liquid N_2 and sensorimotor cortex, cerebellum, medulla, cervical and thoracic spinal cord sections were dissected out onto dry ice and neurochemicals were extracted for *in vitro* study (minimum of 5 per group). No mice were scanned who could not feed independently. A subset of mice were scanned *in vivo* at 9.4T. Brain extracts were run on Bruker 600 MHz spectrometer with TSP or formate as an internal reference for quantification.

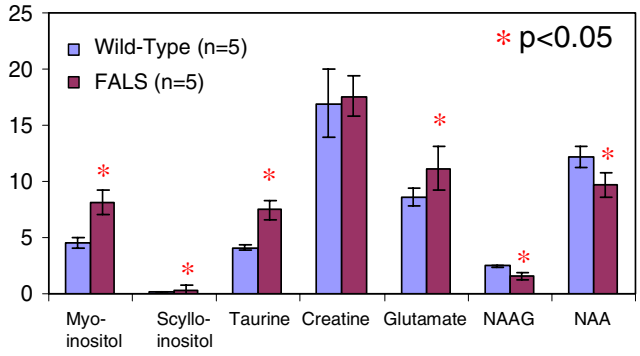
Results There was a pronounced ordering of metabolic abnormalities, as characterized by the magnitude and total number of significant differences with spinal cord > medulla > cortex > cerebellum. The cerebellum showed no differences with WT animals thus providing a good control region. The metabolic abnormalities increased with increasing age. Since the disease starts in the spinal cord it is predicted to manifest the largest abnormalities. At 110 days of age there were significant increases in myo- and scyllo-inositols (79 and 163 %), glutamate (31%) and taurine (80%) compared to WT animals. There were decreases in NAA and NAAG (-20 and -37%). In medulla, the NAA only decreased at 142 days (-37%) but not at 114 days. The glutamate was increased at 114 days but not at 142 days. In motor cortex no changes were noted in NAA, but there were increases in glutamate at 84-114 days, but no changes at 142 days compared to WT. The spinal cord in general has much higher metabolite concentrations than the other brain regioins.

Discussion These results indicate that the spinal cord and medulla are more severely affected than the motor cortex. The metabolic changes evolve with the pathology of the disease and reflect a pattern of increased metabolism at time points early in the pathology (80-115 days). At time points where the animals are partially paralyzed, the metabolic derangement suggests decreased metabolism and neuronal dysfunction. MRS provides an excellent means for following these changes.

A)



B)



C)

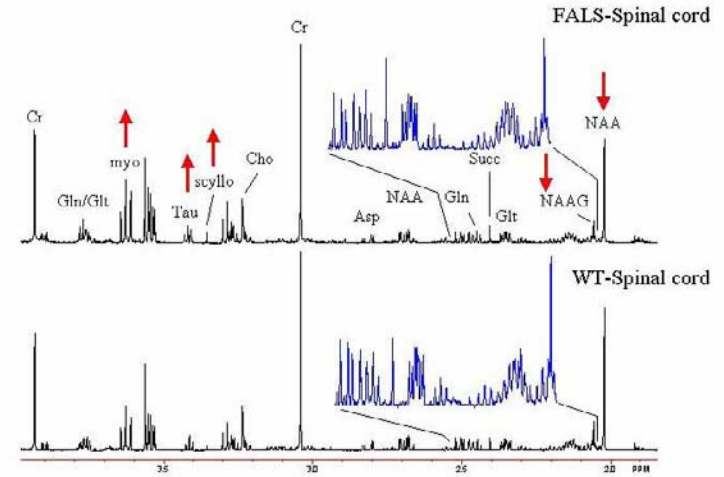


Fig. A) Concentrations (µmol/g wet weight) of selected chemicals for **medulla** in FALS mice as a function of age.

Fig. B) Concentrations (µmol/g wet weight) of selected chemicals for FALS and WT mice at 110 days of age from **spinal cord** extracts.

Fig. C) In vitro Spectra (600MHz) from spinal cord extracts of a FALS mouse and a WT mouse at 110 days of age.