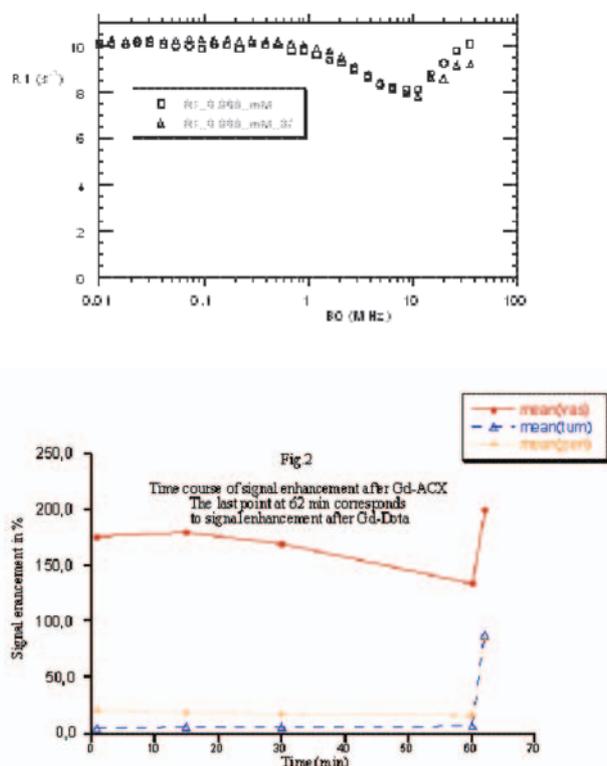


Temperature dependence of the water proton relaxation rate due to ACX-Gd in physiological serum



Scientific Session

11:20 am - 1:00 pm

Sydney

Brain spectroscopy

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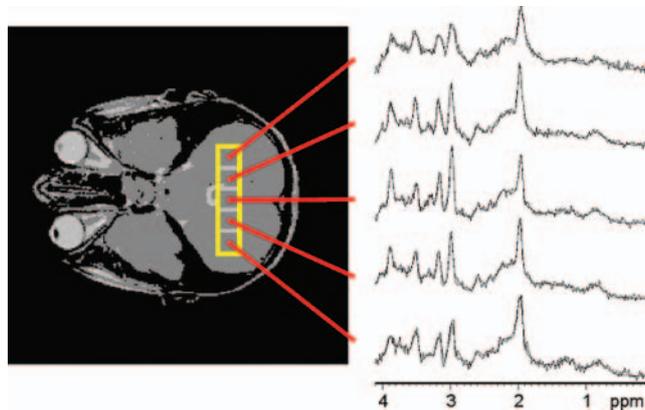
Quantitative ¹H magnetic resonance spectroscopy and neuropsychologic testing in patients with Duchenne muscular dystrophy

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Introduction: Duchenne muscular dystrophy (DMD) is an inherited disease characterized by the disturbance of the protein dystrophin. The resulting reduction in muscle mass leads to inability to walk and to death in early adolescence. The disruption of dystrophin is known to cause cognitive impairment, but details of this mechanism are not clear. Earlier studies in DMD children and the *mdx* mouse found increased cerebellar choline (Ch) ratios [1].

Methods and Subjects: 16 boys with DMD and 19 age-matched healthy boys underwent neuropsychological testing (WISC/WAIS, attention tests, VLM, RVDLT, Rey figure, block tapping, fluency). In 11 patients and 14 controls quantitative ¹H-magnetic resonance spectra were recorded (1.5T, PRESS, 20 ms TE). Single voxel spectra were obtained from language-related parieto-temporal cortex. In cerebellum, 1D CSI spectra were acquired from a 12.5 cm³ PRESS volume (see Figure, 16 phase-encoding steps). Single voxel

data were quantitated as described earlier [2]: LC-Model with 22 model compounds including a macromolecular baseline, quantitation based on unsuppressed water. Quantitation of SI data [3] was based on unsuppressed water and tissue composition information obtained from relaxometry (multi TE IR images). Extrapolation provided tissue content of pure white matter.



Results: Typical CSI spectra of cerebellum and their fit are illustrated in the figure. DMD patients had significantly lower total choline (Ch_{tot}) levels in both ROI's. A small significant involvement of NA (=NAA+NAAG) was found in the parieto-temporal lobe (see Table). In DMD, general intelligence assessment showed a reduced IQ of 86. In DMD patients a highly significant association was found between Ch_{tot}/Cr_{tot} in the parieto-temporal ROI and visuo-spatial memory.

	NAA/tot	Ch/tot	ml/tot	Glx	Cr/tot	NA/Ch	NA/Ch	NA/ml
hilly	8.96±0.08	1.55±0.05	5.18±0.12	10.65±0.19	6.99±0.11	1.29±0.02	5.87±0.19	1.74±0.05
DMD	9.26±0.22	1.30±0.06	4.93±0.13	10.52±0.39	6.69±0.23	1.39±0.03	7.21±0.36	1.88±0.05
	p=0.04	p=0.02						p=0.002

Discussion and Conclusion: In contrast to prior studies [1] we did not find an increase in Ch/NAA. On the contrary, our DMD patients showed a consistent decrease in absolute Ch_{tot} levels in both investigated regions. Most other major metabolites and the macromolecules were indistinguishable from normal in spite of low within-group standard errors (2-5% for most metabolites). The abnormal Ch_{tot} levels are consistent with irregular membrane/myelin turnover in association with the dystrophin deficit, but it is unclear why Ch_{tot} levels can be lower in this study and higher in others. The association between metabolite disturbance and visuo-spatial memory conforms with expectations.

References:

1. Rae C. et al. *J Neurol Sci* 160:148 (1998);
2. Hofmann L, et al. *Magn Reson Med* 48:440 (2002);
3. Vermathen P, et al. 20th ESMRMB, Rotterdam, 2003; #330.

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Recovery of hippocampal metabolism from hypoxia - role of the adenosine A₁ receptor

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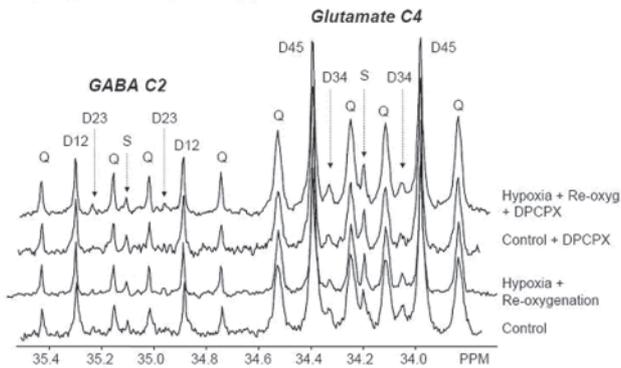
Introduction: Hypoxia compromises brain function. During hypoxia there is a release of both excitatory neurotransmitters that may cause excitotoxicity (*J Neurosci* 20:22), and neuromodulators like adenosine that may have a protective role. Adenosine mainly inhibits transmitter release through activation of adenosine A₁ re-

ceptors (A₁R) (Pharmacol Toxicol 77:299). Hypoxia caused an inhibition of synaptic transmission, which fully recovers on re-oxygenation, and blockade or deletion of A₁R attenuates the recovery of synaptic transmission after the insult (J Neurosci 21:8564; Neurosci 132:575). Acting on A₁R, adenosine has also a homeostatic role modulating neuronal and glial metabolism (J Neurochem 74:327). Thus, we tested the role of the hippocampal A₁R in the metabolic recovery after hypoxia.

Methods: Hippocampal slices (400µm thick, from Wistar rats, 8 weeks old) were rested 45min in a Krebs solution gassed with 95%O₂/5%CO₂. The slices were superfused (3mL/min) with the same solution during 60min, at 37°C, followed by a 90min superfusion either in normoxic or hypoxic conditions (95%N₂/5%CO₂), in the presence of 50µM 4-aminopyridine (4AP) to allow slice stimulation. Then, a group of slices was superfused during 3hours in normoxic conditions in the presence of either unlabelled glucose (5.5mM) and sodium acetate (2mM) or [U-¹³C]glucose and [2-¹³C]acetate, with 4AP present. The superfusions were repeated in the presence of 100nM 1,3-dipropyl-8-cyclopentylxanthine (DPCPX, selective A₁R antagonist) during hypoxia and re-oxygenation and control conditions. Perchloric acid extracts of the slices were lyophilized, dissolved in D₂O and pH adjusted to 7.0. Metabolite concentrations and incorporation of ¹³C atoms into different carbon positions of metabolites (metabolite isotopomers) were determined by ¹H- and ¹³C-NMR spectroscopy (Varian Unity-500 spectrometer, 5mm broadband NMR probe), respectively. Adenine nucleotide concentrations were measured by HPLC analysis and used to calculate energy charge (EC) of the tissue.

Results/Conclusions: Hypoxia altered metabolic pools which recover partially on re-oxygenation. EC was decreased by hypoxia and recovered on re-oxygenation. DPCPX prevented the hypoxia-induced decrease of EC but induced a permanent decrease of EC on re-oxygenation. The TCA cycle of the compartment where glucose is oxidized was not modified in hypoxia plus re-oxygenation, but the presence of DPCPX increases this flux on re-oxygenation. We conclude that the metabolic modifications that occur in hippocampal slices during hypoxia recover upon re-oxygenation, and this recovery is partially prevented by blockade of the A₁R.

Figure 1. Expansions of Representative Glutamate C4 and GABA C2 Resonances in the ¹³C-NMR spectra of PCA extracts from hippocampal slices superfused in the presence of 5.5mM [U-¹³C]glucose, 2mM [2-¹³C]acetate and 50µM 4-aminopyridine.



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H-MRS indicates neuronal involvement in dietary gluten-related ataxia

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Introduction: Sensitivity to ingested gluten is associated with several clinical manifestations including enteropathy, skin disorders

and neurological dysfunction. In terms of neurological dysfunction, both gait and limb ataxia are characteristic (1). This study investigates the cerebellar metabolic status of patients with gluten-related ataxia assessed by H-MRS.

Subjects and Methods: MR was performed at 1.5T (Eclipse, PMS) on 15 patients with sporadic gluten ataxia and 10 neurologically normal, matched controls. A consensus atrophy score (1=none, 2=mild, 3=severe) was assigned to standard MR images by 2 independent, blinded raters. Spectra were obtained from a single (1cmx1cmx1.5cm) cerebellar voxel using short (STEAM: TE=20ms, TR=300ms) and long (PRESS: TE=135ms, TR=1600ms) echo-time techniques. Long TE results are expressed as ratios under the three prominent resonances assigned to Choline (Cho: 3.2ppm), Creatine (Cr: 3.0ppm), and N-Acetyl Aspartate (NAA: 2.02ppm). Short TE results are expressed as the areas under the Cho, Cr, NAA and *myo*-inositol (mi: 3.56ppm) resonances relative to that of unsuppressed water.

Results: Patient and control groups showed significant differences in NAA/Cho (1.25±0.23vs 1.58±0.21, p<0.005); NAA/Cr (1.15±0.18 vs 1.33±0.23, p<0.05) and Cho/Cr (0.93±0.12 vs 0.84±0.07, p<0.05) at TE=135ms and NAA (0.63±0.08 vs 0.79±0.10, p<0.001) at TE=20ms. Three of the 15 patients had severe, 5 had mild and 7 had no atrophy. None of the controls had severe, 2 had mild and 8 had no atrophy. Mean NAA resonance areas are plotted against atrophy score for the gluten ataxia group in figure 2. No significant difference or trend was observed with atrophy score within the patient group.

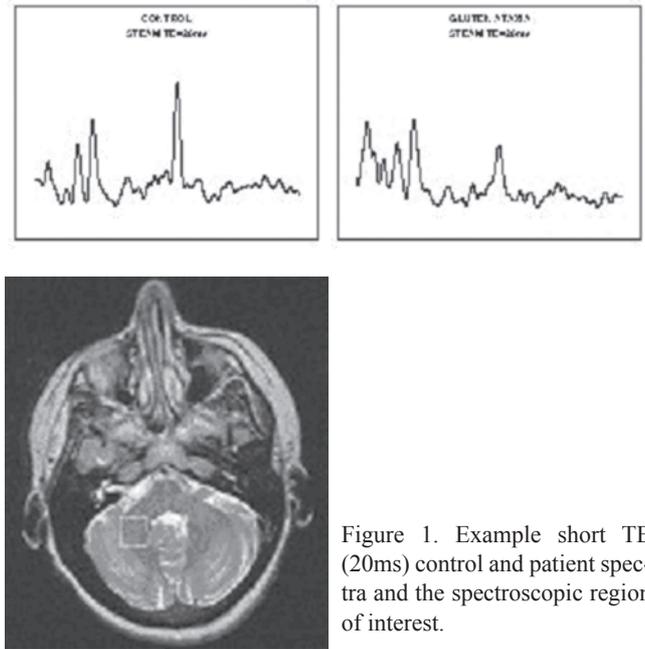


Figure 1. Example short TE (20ms) control and patient spectra and the spectroscopic region of interest.

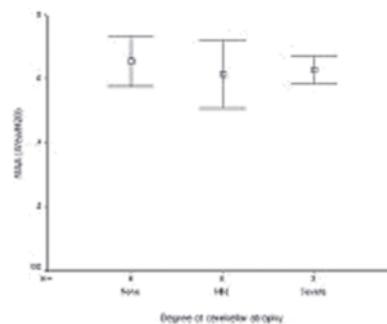


Figure 2. Mean NAA normalised to unsuppressed water as a function of atrophy score for the patient group.