

Imaging the in vivo effect of hyperammonemia in the rat brain: a Spectroscopic Imaging and Diffusion Tensor Imaging study

Cristina Cudalbu¹, Nicolas Kunz¹, Bernard Lanz¹, Yohan Van de Looij¹, Vladimir Mlynárik¹,
and Rolf Gruetter^{1,2}

¹Laboratory for Functional and Metabolic Imaging (LIFMET), Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland, ²Departments of Radiology, Universities of Lausanne and Geneva, Switzerland

Objectives:

Ammonia is a neurotoxin that is implicated in the pathogenesis of hepatic encephalopathy (HE). Brain edema represents a major complication. In hyperammonemic (HA) conditions, glutamine is generated in astrocytes from ammonia and glutamate in a reaction catalyzed by glutamine synthetase (GS). In vitro observations suggested that during HA, alterations in brain metabolites other than glutamine can occur (1,2). Diffusion tensor imaging (DTI) measures the relative translational motion of water proton across cell membrane, which is expressed as the ADC value. Changes in ADC reflect the presence of edema. The in vivo spatial distribution of brain metabolites can be measured using proton spectroscopic imaging (SI). The aim of the study was: 1) to assess the effects of HA per se in the rat brain by DTI; 2) to image for the first time the in vivo effect of hyperammonemia per se on 12 brain metabolites (i.e. Gln, Glu, tCr, tCho, Ins, Tau, Lac, NAA+NAAG, Lac, etc) in different brain regions and the net glutamine synthesis rates.

Methods:

Experiments were performed on a 9.4T MRI system using SD rats. NH₄Cl was infused (4.5mmol/h/kg) for 6h. Diffusion tensor acquisitions were performed (3) and diffusivity values (ADC, FA) were derived from the tensor. ADC was measured in ROIs positioned in: Cortex (Cx), Striatum (St), Hippocampus (Hip) and Ventricles (Ven). Ventricles sizes were also calculated on the ADC maps with a threshold set to 10mm²/s. Metabolic maps were obtained using short-echo-time proton-spectroscopic-imaging (4).

Results:

The results are presented in Fig 1. ADC measurements showed a decrease along the infusion (6%), significant only 6 hours after infusion. In addition, an increase of the ventricles size was visible ($V_{\text{before}}=18 \pm 6\text{ml}$, $V_{+6\text{h}}=31 \pm 13\text{ml}$, $p<0.05$). The increase in the Gln pool at different time

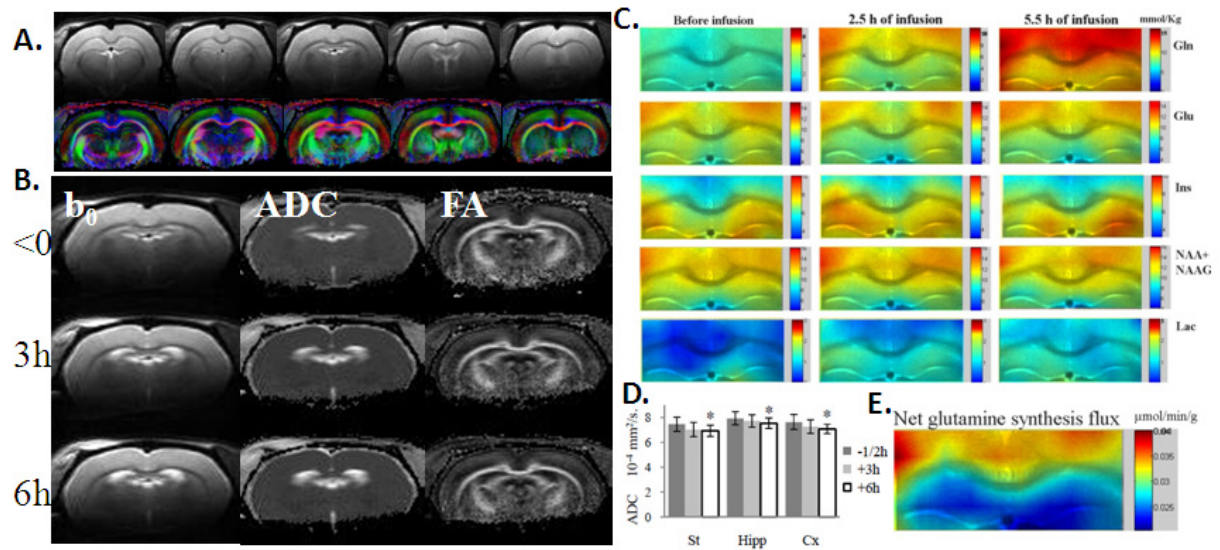
points during infusion was apparent from the maps. The Gln concentration increased more in cortex than in hippocampus (5.5hh of infusion $16.2 \pm 2.7 \text{ mmol/kg}_{\text{ww}}$ Cx and $11.5 \pm 1.2 \text{ mmol/kg}_{\text{ww}}$ Hip, $p=0.03$). The maps of the other brain metabolites did not show any visible difference before and after ammonia infusion. From the linear fit of the time-evolution of Gln we obtained a net glutamine synthesis rate of $0.039 \pm 0.007 \mu\text{mol/min/g}$ Cx and $0.024 \pm 0.007 \mu\text{mol/min/g}$ Hip ($p=0.05$).

Discussion:

We propose that HA per se induces late in time a mild brain edema, as indicated by the decrease in ADC at 6h. Nevertheless, the origin of the ventricles increase and the presence of mild brain edema remain unclear and will need further investigations. High resolution metabolic maps enabled to observe the in vivo spatial distribution of 12 metabolites in various brain structures under HA. Contrary to other models of HA associated with experimental acute liver failures (1,2), no changes in spatial distribution of metabolites were observed except for Gln. The net glutamine synthesis rates were significantly higher in the cortex than in the hippocampus.

References:

[1] Zwingmann C, J Neurosci Res. 85:3429, 2007. [2] Rao KV et al, Metab Brain Dis. 16:67, 2001. [3]Kunz N, Proceedings ISMRM 2008. [4] Mlynárik V *et al.* Magn Reson Med. 59:52, 2008.



A) Images acquired with the semi-adiabatic SE-EPI before infusion, with the diffusion coefficient maps. b_0 image ($b = 0 \text{ mm}^2/\text{s}$) and color encoded map (Cmap). B) b_0 image ($b = 0 \text{ mm}^2/\text{s}$), diffusion tensor trace (ADC) and fractional anisotropy (FA) maps acquired before infusion (<math>t < 0</math>), +3h after infusion, +6h after infusion. C) Metabolic maps of Gln, Glu, Ins, NAA+NAAG, Lac superimposed on the anatomical T_{2w} images and acquired at different time points during ammonia infusion. D) Mean ADC values before infusion, 3h and 6h after infusion in the striatum (St), hippocampus (Hipp) and cortex (Cx). *: $p < 0.05$ compared to control. E) Net glutamine synthesis rates imaged over the VOI and superimposed on the anatomical T_{2w} images.