Preserved Whole Brain N-acetylaspartate during Mild Hypercapnia Challenge

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Introduction: N-Acetylaspartate (NAA) is the most prominent metabolite observed on proton MR spectroscopy (^{1}H MRS).[1] NAA is considered as a putative neuronal marker of neuronal cell density and viability, and is often used in various CNS disorders to indicate the disease severity and progression.[2] NAA is produced in neuronal mitochondria and the normal NAA concentrations is in the range of 8-9 mmol/kg.[2] Although NAA concentrations are decreased in many pathological conditions,[3] few studies have observed that concentration of NAA remains stable in response to some physiological challenges.[4,5] Carbon dioxide (CO_2) is a potent vasodilator and has been known to cause cerebral blood flow (CBF) and blood oxygenation changes.[6] In this study, we have evaluated the whole brain NAA (WBNAA) changes during hypercapnia breathing using a fast and validated WBNAA ^{1}H MRS technique[7] in healthy volunteers. The effect of hypercapnia on brain hemodynamics (i.e. CBF) and venous oxygenation (Yv) are also measured to ascertain the hypercapnia effects in these volunteers.

Methods: A cohort of eleven healthy male adults was enrolled for this study. All subjects underwent WBNAA, T2-relaxation under spin tagging (TRUST) and pseudo continuous arterial spin labeling (pCASL) under both normocapnia (room air) and hypercapnia conditions on a 3T MR scanner. Hypercapnia was induced by 5% carbon dioxide (CO_2, mixed with 21% oxygen gas, and 74% nitrogen gas) and was administered via a Douglas bag with a valve to switch between room air and CO_2 air. Venous oxygenation levels of sagittal sinus were studied using TRUST technique. CBF measurement was performed with multi-slice pCASL sequence based on single shot gradient-echo EPI. Absolute value of WBNAA was computed in institutional units (IU). TRUST and pCASL data were processed using in-house MATLAB scripts based on algorithms described previously.[8,9]

Results: Figure 1 demonstrates representative images from a normal subject displaying WBNAA spectra at pre-hypercapnia (baseline), and hypercapnia conditions. There was 0.2% change in the WBNAA concentration from normocapnia to hypercapnia condition and this variation was not significant ($p>0.05$). However, there was significant effect of hypercapnia on global gray matter CBF with a 17.59% increase in CBF from normocapnia (45.22±6.81 ml/100g/min) to hypercapnia condition (62.82±8.7 ml/100g/min, $p<0.05$). Over a group of 12 subjects, normocapnia CPMG-T2 in the sagittal sinus was found to be 54.48±13.14 ms and the corresponding venous oxygenation was 56.31±7.33%. However, subsequent to hypercapnia, significant increases in CPMG-T2 (85.66±11.27ms) and venous oxygenation (72.0±4.17%) were observed. Variations in the different parameters at two conditions are shown as box and whisker plots in figure 2.

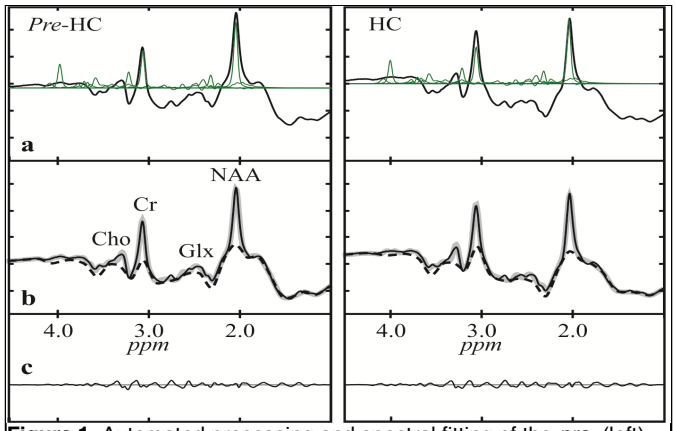

Figure 1. Automated processing and spectral fitting of the *pre-* (left) and during- (right) WBNAA results from one subject, all on the same intensity and chemical shift (*ppm*) scales. Top, **a**: Whole-head ^{1}H-spectrum (thin black line) and model functions (green lines). Center, **b**: Whole-head ^{1}H-spectrum (thin black line), estimated baseline (dashed line) and fitted (metabolites+baseline) estimate (thick gray line). Bottom, **c**: Residual signals [data - (metabolites + baseline)]. Note: *(i)* The similarity of the *pre-,* HC and *post*-HC spectra, suggesting minimal effect on the brain NAA by this philological challenge.

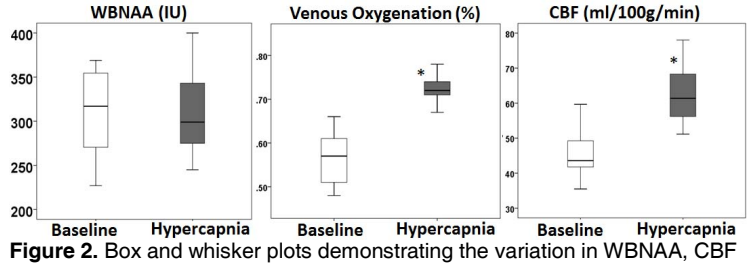

Figure 2. Box and whisker plots demonstrating the variation in WBNAA, CBF and venous oxygenation at baseline and hypercapnia conditions. Significant increases in venous oxygenation and in CBF were observed. However, WBNAA showed not significant change.

Discussion: We demonstrated that mild hypercapnia induces no significant variation in the WBNAA concentration despite significant elevations in global GM CBF concomitantly with venous oxygenation. The preserved concentration of WBNAA indicates that neuronal biochemical responses to markedly increased cerebral blood flow and increased blood CO_2 levels are minimal and structural and functional integrity of neurons remains unaltered. Since ATP and NAA synthesis within mitochondria are coupled together,[2] it might be considered that mild hypercapnia would not impair neuronal mitochondrial function despite a slight increase (not significant) in WBNAA following hypercapnia. In summary, our study suggests that neuronal metabolism and vascular hemodynamics may have different response to mild hypercapnia and WBNAA likely represents a sensitive marker to pathological conditions that are beyond the physiological stress.

Acknowledgement: This work was supported by NIH Grants EB01015, NS029029-20S1, NS076588, and EB008387 and performed under the rubric of the Center for Advanced Imaging Innovation and Research (CAI2R, www.cai2r.net), a NIBIB Biomedical Technology Resource Center (NIH P41 EB017183).

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