

MR Spectroscopy of Hypobaric Hypoxia Induced Changes in Rat Brain Hippocampus using 7Tesla

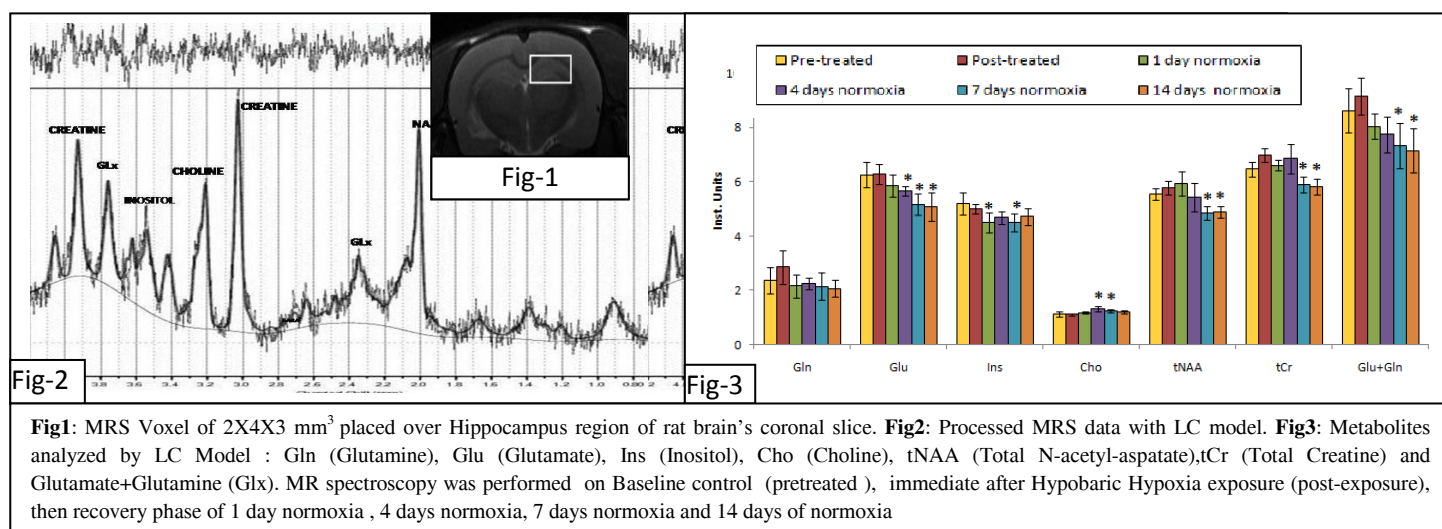
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Introduction: High altitude areas have air at low pressure which affects human health due to low oxygen availability to their lungs and all vital organs. Under these hypoxic conditions, brain is most adversely affected. Mountain trekkers and army troops working at high altitude are more vulnerable to high altitude sickness¹. Hippocampus is most sensitive to hypobaric hypoxia, undergoes neurodegeneration and oxidative stress². MRS is a powerful tool to study the metabolic alterations occurring in brain due to high altitude stress. It is of utmost importance to study changes at metabolite level in hippocampus due to hypobaric hypoxia in order to understand its pathophysiology. This in turn can help in identifying potential metabolic biomarkers and early detection due to hypobaric hypoxia.

Objective: To study the temporal metabolic changes in Rat Brain due to acute high altitude stress & recovery phase using MR Spectroscopy at 7 Tesla.

Materials and method: 11-12 weeks male Sprague Dawley rats (n=6, 250±30g) were exposed to hypobaric hypoxia of 22,000 feet in climatic hypoxia chamber for 48hrs with temperature & humidity regulated at 25±1°C & 55±1% respectively. MR spectroscopy experiments were carried out on hippocampus region of rat brain before (control) & after hypobaric hypoxia for 48 hrs. Recovery phase was also seen at normal room temperature and pressure (i.e. normobaric normoxia) on day 1, day 4, day 7 and day 14. Voxel of 2×4×3 mm³ was placed over hippocampus (Fig-1) & Proton MR spectra was acquired. LC model (Fig-2) was used for automatic quantification of various metabolites present in the acquired proton MR spectra. Changes in brain metabolites levels (institutional units) in response to hypobaric hypoxia was plotted against time and expressed as means ± SD at each time point (Fig-3). Changes in particular metabolite between various time points were compared by one-way repeated-measures ANOVA followed by an all-pairwise Bonferroni's multiple comparison post hoc test using Sigmaplot.



Results: Comparison between different time point groups with pretreated controls showed significant decrease in Glutamate levels after 4 days, 7 days & 14 days of normoxia (i.e. 4, 7 and 14 days at room temperature conditions) post exposure to 48hrs of hypobaric hypoxia (Figure 3). Significant decrease in Myo-inositol was observed after 1 day and 7 days of normoxia post exposure. tNAA, tCr and Glu+Gln levels were found to be significantly low at 7 and 14 days of normoxia while cholines were increased at 4 and 7 days of normoxia after exposure to hypobaric hypoxia.

Discussion: In vivo MRS results show significant decrease in levels of glutamate post exposure which might be a consequence of damage in glutamatergic neurons as they are particularly sensitive to Hypoxia². This damage is irreversible as Glutamate levels could not recover back in the Hippocampus region. The myo-inositol is predominantly located within Astrocytes and is a precursor for the Phosphatidylinositol (PI) second messenger system that is also presumed to act as an osmoregulator³. Significant decrease in levels of myoinositol can be correlated with altered astrocytic cellular metabolism. Our results showed a significant decrease in neuronal marker NAA which can be correlated to axonal degeneration or loss at 7th day after hypoxic exposure⁴. Creatine level is known to be constant in normal brain. Under hypoxic stress creatine levels decreases which can be the result of defect in the intracellular energy metabolism⁵. Significant increase in choline levels at 4 and 7 days after exposure to hypobaric hypoxia which indicates increased cellular membrane turnover most probably due to demyelination.

Conclusion: MRS study on rat brain reveals a subtle interplay of functional metabolites and pathways leading to an understanding of systemic response to external stimuli, such as high altitude stress. Results show deleterious effects of acute Hypobaric Hypoxia occurring at metabolite level which appears to be due to neuronal loss & altered Astrocyte metabolism. These results can be correlated with other in vitro spectroscopy, biochemical, analytical & molecular parameters to detect early biomarkers for high altitude stress injuries in humans which can further be used for risk assessment & early diagnosis.

References:

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