Metabolic Alterations in Rat Brain due to Chronic High Altitude Stress: A 1H-MRS study

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Target Audience: Researchers, Clinicians and Students.

Purpose: Hypobaric hypoxia, a condition which prevails at high altitude, results in reduced cerebral oxygenation. Brain under hypoxic stress induces neuropathological conditions including acute mountain sickness and high altitude cerebral edema.[1] Hippocampus region of brain is most sensitive to such hypoxic condition, which undergoes neurodegeneration and oxidative stress.[2] MR Spectroscopy is a powerful tool to study the metabolic alterations occurring in brain under *in vivo* conditions. MR Spectroscopy may yield valuable information of neuro-metabolic alterations in response to the chronic exposure to high altitude. Further, this study will help in better understanding of hypobaric hypoxia induced pathophysiology and progression. This in turn can help in identifying potential metabolic biomarkers and early detection due to hypobaric hypoxia.

Objective: To study the metabolic changes in Rat Brain due to chronic high altitude stress using MR Spectroscopy at 7 T.

Materials and Method: Twenty one male Sprague Dawley rats (11-12 weeks old) were divided into 3 groups (7 rats each group). Group 1, 2 & 3 were exposed to hypobaric hypoxia at 22,000 feet for 7, 14, and 21 days respectively in climatic hypoxia chamber. Temperature & humidity were regulated at 25±1°C & 55±1% respectively. MR spectroscopy (PRESS sequence with TR/TE=2500/20 ms) experiments were carried out on hippocampus region of rat brain before (control) & after hypobaric hypoxia for each group on Bruker 7T. Voxel of 2×4×3 mm3 was placed over hippocampus (Fig-1) & Proton MR spectra were acquired. LC model 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-2). Changes in each metabolite between pre and post exposure for each group were compared separately by paired student's t-test using SPSS.

Results: Inositol and choline showed significant decrease after 7 and 14 days of hypoxic exposure. A significant increase was found in taurine and creatine after 14 and 21 days of hypobaric hypoxia. Glu+Gln showed significant decrease after 14 days of hypoxia. There was no significant change in NAA levels.

Discussion: In vivo MRS results show significant decrease in levels of inositol after 7 and 14 days of chronic hypoxia which may indicate osmoregulation or altered astrocyte cellular metabolism.[3] Increment in taurine after 14 and 21 days of chronic hypoxia exposure might be linked to its protective effect by counteracting the effects of excitotoxicity, hence rescuing from neuronal damage.[4] Choline levels were decreased after 7 and 14 days of hypoxia. Previous reports says decreased choline may reflect better healing ability of cerebral tissue.[5] Total Creatine levels were increased after 14 and 21 days hypoxia, though few brain pathology reported increase in total creatine,[6] mechanism is still unclear which needs to be further investigated. Glutamate+Glutamine (Glu+Gln) levels were decreased after 14 days hypoxia which may reflect altered glutamate metabolism. NAA levels did not show any significant change which may be due to rescue of cerebral tissue from neuronal damage.

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 effects of chronic hypobaric hypoxia occurring at metabolite level which appears to be an attempt to rescue brain tissue against neuronal loss. Though it is too early to predict complete recovery of cerebral tissue which needs to be further studied, these results can further be correlated with in vitro High resolution NMR spectroscopy, biochemical and analytical analysis 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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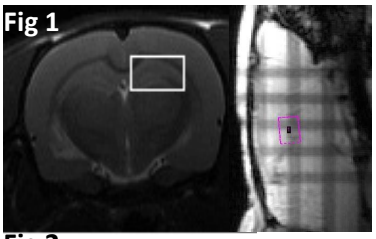

Fig1: MRS Voxel of 2X4X3 mm^3 placed over Hippocampus region of rat brain by locating with the help of coronal and saggital slices.

Fig 2

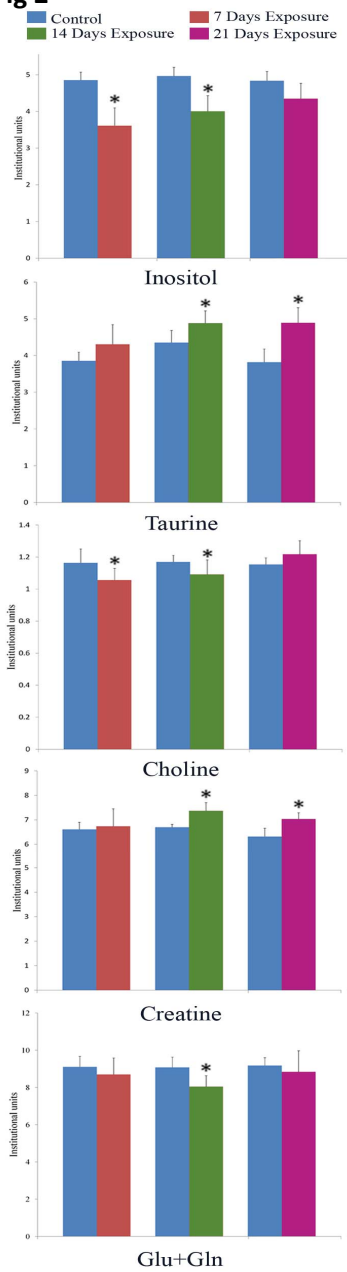

Fig2: Variation in metabolite concentration analyzed by LC Model on MRS data for pre and post Hypobaric Hypoxia exposure of 7, 14 and 21 days.
* statistically significant levels of $P \leq 0.05$ w.r.t pre-exposed baseline controls