



Molecular Mechanism of Hypobaric Hypoxia Induced Neurophysiological Distresses

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DESCRIPTION

Hypobaric Hypoxia (HH) is an environmental stress encountered at high altitude in the Older adults. This arises due to reduced partial pressure of oxygen (pO_2). The low pO_2 leads to decrease in alveolar and arterial oxygen tension and eventually translates into inadequate oxygen transport to the tissues thus resulting in cellular hypoxia. HH condition causes systemic stress affecting various organ systems. Among those, the Central Nervous System (CNS) is highly vulnerable to hypoxic insult, owing to its high metabolic rate and limited capacity of oxygen storage. However, sustained HH results in multiple pathophysiological consequences, which range from moderate condition like AMS (Acute Mountain Sickness) to severe HACE (High Altitude Cerebral Edema). Other HH induced symptoms include insomnia, headache, alteration of mood, ophthalmologic disturbance, fall in psychomotor performance and cognitive function like learning and memory impairment etc.

The occurrence of HH induced disease varies between people and also largely depends on chronicity of exposure, altitude and rate of ascent. Some of the previous studies have variously attributed the pathophysiological observations to change in hemodynamics, free radical generation, neurotransmitter alteration, and loss of neurons by apoptosis in hippocampus and dendritic atrophy in hippocampal pyramidal neuron culminating in learning and memory deficit. Compromised Blood Brain Barrier (BBB) permeability accompanied by vasogenic and cerebral edema has also been reported. Despite notable work in this area during past decade, several basic questions pertaining to the patho-etiology and molecular mechanisms underlying this condition continue to remain unsolved.

For instance, it is not known if the loss of neurons is 'primary' in response to hypoxia or 'secondary' due to BBB dysfunction. Also, it is still unresolved that how HH affects cellular constituents of brain, namely neurons, glia and endothelial cells. Current treatments for HH induced cognitive deficit are limited

and no treatment has yet conclusively shown to alter disease progression. A better understanding of early-molecular triggers, which drive disease progression, is needed in order to develop more targeted therapies to impede HH induced conditions. Recent work has established H_2S as the third gasotransmitter besides NO (Nitric oxide) and CO (Carbon monoxide). H_2S is a pleiotropic regulator of systemic and brain vascular homeostasis. Its role in various cellular functions has been described as a secondary messenger, antioxidant, sulfhydrating agent, vascular tone regulator, angiogenic and neurotransmitter.

Further, H_2S facilitates long-term potentiation and regulates intracellular calcium concentration in brain cells. Additionally, H_2S has antioxidant, antiapoptotic, and anti-inflammatory properties against various neurodegenerative disorders such as stroke, Alzheimer's disease, and vascular dementia. In this study 'Morris Water Maze' tests was utilized to establish a temporal window during which reproducible, quantifiable deficit in 'spatial reference memory' manifests in our rat model system, exposed to simulated hypobaric hypoxia. We found spatial memory impairment post 7-day HH exposure in parallel to occurrence of cell death in pyramidal neurons. It is however not known, what is the temporal scheme of events, which eventually results in the cognitive impairment and neuronal death. To understand this, we generated time dependent transcriptome signatures of hippocampal responses. Specific networks regulating Extracellular Matrix (ECM) dynamics and myelination of neurons besides expected biological themes like response to hypoxia, steroid hormone, and dynamics of circulatory system were revealed by Pathway mining strategies.

CONCLUSION

Furthermore, to understand the chronology of physiological as well as molecular perturbations during HH-induced neuro-pathological effects, we subjected time course expression data to an unbiased statistical co-expression networking tool, Weighted Gene Co-expression Network Analysis (WGCNA), which can be used for finding clusters (modules) of highly correlated genes.

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These modules tend to contain genes of similar biological functions. This analysis identified 6 modules with unique temporal expression patterns. The GO (Gene Ontology) analysis of modules suggested perturbation of various components of glio-vascular unit. Interestingly, it was observed that modules composed of GO term related to vascular components shared maximum perturbation at day 1 and modules composed of GO term related to neurons showed maximum perturbation at day 7. To validate biological inferences from gene expression data and network analysis, ultrastructural changes in rat brain during HH was investigated.

High-resolution EM image analysis revealed evidence for Astrocyte end feet swelling and decrease in the width of basal lamina in HH exposed rat brain. Additional experiments including substrate zymography, Immunohistochemistry (IHC) and Immunofluorescence (IF) assays were performed to substantiate our observation. Along with time-dependent increase in vWF expression in hypoxic rat brain, increased expression of soluble ICAM-1 (Intercellular Adhesion Molecule 1) in plasma was observed, suggesting endothelial activation. A significant increase in the activity of MMP in brain extracts from animals exposed to 1 day of hypobaric hypoxia was also found. This activity, however, decreased in the subsequent time points analyzed. Increase in GFAP (Glial Fibrillary Acidic Protein) staining post HH exposure indicated glial activation as well. Endothelial dysfunction, erosion of basement membrane and

activation of Astrocytes strongly suggested perturbation of 'BBB function'. This phenomenon was also evident as segregation of Laminin and Aqp signals as indicated in confocal images.

The likely involvement of vascular injury prompted us to H₂S, which is involved in multiple cellular functions as well as plays a critical role in cerebral autoregulation. Post HH exposure, H₂S levels in rat brain was measured. Interestingly, significant decrease in the levels of H₂S in response to HH was reproducibly observed. H₂S augmentation was found to prevent hypobaric hypoxia induced endothelial and glial activation as indicated by expression of sICAM in plasma samples and GFAP in brain sections.

In striking contrast to the animals exposed to HH without NaHS an H₂S donor, the Laminin-Aqp signals perfectly localized in the brain sections of animals receiving NaHS, prior to HH. We thus inferred that NaHS-mediated maintenance of H₂S levels prevented HH-induced loss of Glial-Vascular homeostasis. Taken together, our work resolved origin/nature of injury during hypobaric hypoxia. It revealed early glial-vascular unit dysfunction, which progresses to perturb the neurovascular unit and secondary neuronal loss with neuro-pathophysiological effects during HH. In addition, the role of H₂S signaling in preservation of brain vascular homeostasis under HH condition was observed.