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Altered Proteostasis Contributes to Skeletal Muscle Atrophy during Chronic Hypobaric Hypoxia: An Insight into Signaling Mechanisms

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Abstract : Muscle represents about ¾ of the body mass, and a healthy muscular system is required for human performance. A healthy muscular system is dynamically balanced via the catabolic and anabolic process. High altitude associated hypoxia altered this redox balance via producing reactive oxygen and nitrogen species that ultimately modulates protein structure and function, hence, disrupts proteostasis or protein homeostasis. The mechanism by which proteostasis is clinched includes regulated protein translation, protein folding, and protein degradation machinery. Perturbation in any of these mechanisms could increase proteome imbalance in the cellular processes. Altered proteostasis in skeletal muscle is likely to be responsible for contributing muscular atrophy in response to hypoxia. Therefore, we planned to elucidate the mechanism involving altered proteostasis leading to skeletal muscle atrophy under chronic hypobaric hypoxia. Material and Methods-Male Sprague Dawley rats weighing about 200-220 were divided into five groups - Control (Normoxic animals), 1d, 3d, 7d and 14d hypobaric hypoxia exposed animals. The animals were exposed to simulated hypoxia equivalent to 282 torr pressure (equivalent to an altitude of 7620m, 8% oxygen) at 25°C. On completion of chronic hypobaric hypoxia (CHH) exposure, rats were sacrificed, muscle was excised and biochemical, histopathological and protein synthesis signaling were studied. Results-A number of changes were observed with the CHH exposure time period. ROS was increased significantly on 07 and 14 days which were attributed to protein oxidation via damaging muscle protein structure by oxidation of amino acids moiety. The oxidative damage to the protein further enhanced the various protein degradation pathways. Calcium activated cysteine proteases and other intracellular proteases participate in protein turnover in muscles. Therefore, we analysed calpain and 20S proteosome activity which were noticeably increased at CHH exposure as compared to control group representing enhanced muscle protein catabolism. Since inflammatory markers (myokines) affect protein synthesis and triggers degradation machinery. So, we determined inflammatory pathway regulated under hypoxic environment. Other striking finding of the study was upregulation of Akt/PKB translational machinery that was increased on CHH exposure. Akt, p-Akt, p70 S6kinase, and GSK- 3β expression were upregulated till 7d of CHH exposure. Apoptosis related markers, caspase-3, caspase-9 and annexin V was also increased on CHH exposure. Conclusion: The present study provides evidence of disrupted proteostasis under chronic hypobaric hypoxia. A profound loss of muscle mass is accompanied by the muscle damage leading to apoptosis and cell death under CHH. These cellular stress response pathways may play a pivotal role in hypobaric hypoxia induced skeletal muscle atrophy. Further research in these signaling pathways will lead to development of therapeutic interventions for amelioration of hypoxia induced muscle atrophy.

Keywords : Akt/PKB translational machinery, chronic hypobaric hypoxia, muscle atrophy, protein degradation
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