Impaired adaptive responses to hypoxia in patients with diabetes

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The main therapeutic challenge in diabetes is represented by the devastating complications of the disease. Tissue hypoxia not only occurs in acute ischemic events but also is common in most organ and tissues in diabetes and plays an important role in diabetes complications. A central pathogenic role has been identified in the impaired activation of Hypoxia-inducible factor-1 (HIF-1) which functions as a master regulator of the adaptive responses to hypoxia and is inhibited by hyperglycemia in diabetes. In this study, we aim to investigate the change in the adaptive responses to hypoxia in patients with diabetes.

15 patients with Type 1 diabetes and 15 healthy matched controls were exposed to intermittent hypoxia (IH) for one hour, consisting of five hypoxic episodes (13% O_2, 6 min) followed by normoxic episodes (20.9% O_2, 6 min). Upon IH exposure, patients with diabetes had significantly lowered baroreflex sensitivity (BRS). Higher plasma SDF-1alpha levels were induced by IH in healthy controls, but not in patients with diabetes. The number of endothelial progenitor cells (EPC) in circulation increased in healthy subjects after IH, but decreased in patients with diabetes. Before IH exposure, patients with diabetes had significantly higher ROS levels in blood than healthy controls. IH did not change ROS levels in healthy controls, but significantly increased ROS levels in patients with diabetes.
In order to evaluate the molecular mechanisms of the responses to hypoxia, we isolated peripheral blood mononuclear cells (PBMC) and analyzed the expression of microRNA-210 (miR-210), a well-known target of HIF-1 signaling. MiR-210 expression was induced by hypoxia in PBMC from control subjects, but did not change in patients with T1D, indicating impaired HIF-1 activation by hypoxia in diabetes. In healthy subjects, transcriptome profiling of PBMC revealed significant changes in the expression of genes involved in adaptive responses to hypoxia, such as modulation of mitochondrial function and metabolism. However, these changes were absent in patients with diabetes.

These data showed significantly complex impairment of the responses to hypoxia in patients with diabetes upon exposure to intermittent hypoxia. The impaired adaptive responses to hypoxia may play a pivotal pathogenic role for the development of diabetes complications and in the reaction to acute ischemic events.