Dyshomeostasis of Pancreatic Amylin Provokes Hypoxia and Accelerates Aging

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Abstracts will be considered for both poster and platform presentations

Stroke/Neurovascular

Capillary function and oxygen-carrying capacity of red blood cells (RBCs) decline in type-2 diabetes exacerbating the risk of hypoxia and organ malfunction. Amylin is a β-cell hormone that forms pancreatic amyloid in patients with type-2 diabetes and its blood level is elevated in prediabetes. Given the amyloidogenicity of human amylin, we hypothesized that hyperamylinemia increases the risk of hypoxia by provoking microcirculatory disturbances. Using rats with pancreatic overexpression of human amylin (HIP rats) and transfusion with RBCs from diabetic HIP rats into normal rats, we show that the transition from prediabetes to diabetes is associated with amylin deposition in capillaries and RBCs, which increases RBC to endothelial cell adherence, decreases RBC hemoglobin and activates hypoxia-inducible factors in endothelial cells leading to arginase-nitric oxide dysregulation. Prediabetes-induced amylin dyshomeostasis accelerates aging in HIP rats with multi-organ impairments and increased mortality. Upregulation of epoxyeicosatrienoic acids, which are lipid mediators formed by endothelial cells, mitigates amylin deposition in capillaries and hypoxia. In humans, amylin deposition in RBCs increases with aging in association with type-2 diabetes, heart failure, cancer and stroke. Thus, prediabetes-induced amylin dyshomeostasis impairs capillary function and oxygen-carrying capacity of RBCs; amylin-loaded RBCs can initiate pathological processes that are involved in pathological aging.