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Regulation of insulin metabolism by intermittent hypoxia: Molecular mechanisms

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Epidemiologic studies suggest that Type 2 diabetes (T2D) is one of the most common co-morbidities associated with obstructive sleep apnea (OSA). Intermittent hypoxia (IH) is a hallmark feature of OSA. In the present study, we examined the effects chronic IH on insulin metabolism in C57BL6 mice. IH-exposed mice exhibited elevated levels of fasting plasma insulin, but comparable glucose levels indicating that IH leads to insulin resistance. Basal insulin secretion was elevated in IH treated mice and pancreatic islets exposed to IH *in vitro*. IH had no significant effect on pancreatic beta cell morphology. However, insulin content was significantly decreased ($P<0.01$) and proinsulin levels were increased ($P<0.01$) in IH treated pancreatic islets, suggesting that IH impairs proinsulin processing. Glucose-stimulated insulin secretion (GSIS) was severely impaired in IH exposed mice and isolated islets exposed to IH *in vitro*. Mitochondrial reactive oxygen species (ROS) levels were elevated in beta cells exposed to IH. Treating IH exposed mice with mito-tempol, a scavenger of mitochondrial ROS prevented the augmented insulin secretion and restored the proinsulin levels to controls. IH increased HIF-1α levels in pancreatic beta cells. Treating pancreatic islets with either YC-1 or digoxin, which inhibit HIF-1α accumulation, prevented IH-evoked augmented insulin secretion and ROS levels. Similar results were obtained with CIH exposed mice partially deficient in HIF-1 α. These results demonstrate that IH leads to pancreatic beta cell dysfunction manifested by augmented basal insulin secretion, insulin resistance, defective proinsulin processing and impaired GSIS. It is suggested that HIF-1 mediated ROS is an important cellular mechanism mediating the effects of IH on pancreatic beta cell function.

Biography

Jayasri Nanduri received Ph.D. degree from Andhra University, India, and post doctoral training from Nobel Institute for Biochemie, Stockholm. She joined as a Research Associate in the Department of Medicine at Case Western Reserve University, Cleveland, OH and was promoted to Assistant Professor. She is currently at the University of Chicago, as an Associate Professor in the Institute of Integrative Physiology. Her research focuses on the role of hypoxia-inducible factors (HIF-1 and HIF-2) in cellular and systemic responses to IH with special emphasis on IH altered β-cell function. She is an author on 37 peer reviewed papers and a manuscript reviewer for a number of journals.

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