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Insulin Induces Transcription of VEGF in Arnt-dependent but HIF-1α-independent Pathway

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Hypoxia is a pathophysiological condition that occurs during injury, ischemia, and stroke. Hypoxic stress induces the expression of genes associated with increased energy flux, including the glucose transporters Glut1 and Glut3, several glycolytic enzymes, nitric oxide synthase, erythropoietin and vascular endothelial growth factor. Induction of these genes is mediated by a common basic helix-loop-helix PAS transcription complex, the hypoxia-inducible factor-1α (HIF-1α)/ aryl hydrocarbon receptor nuclear translocator (ARNT). Insulin plays a central role in regulating metabolic pathways associated with energy storage and utilization. It triggers the conversion of glucose into glycogen and triglycerides and inhibits gluconeogenesis. Insulin also induced hypoxia-induced genes. However the underlying mechanism is unestablished. Here, we study the possibility that transcription factor HIF-1α is involved in insulin-induced gene expression. We investigate the mechanism that regulates hypoxia-inducible gene expression in response to insulin. We demonstrate that insulin increases the transcription of hypoxia- inducible gene. Insulin-induced transcription is not detected in Arnt defective cell lines. Under hypoxic condition, HIF-1α stabilizes but does not under insulin treatment. Insulin-induced gene expression is inhibited by presence of PI-3 kinase inhibitor and Akt dominant negative mutant, whereas hypoxia-induced gene expression is not. ROS inhibitor differently affects insulin-induced gene expressions and hypoxia-induced gene expressions. Our results demonstrate that insulin also regulates hypoxia-inducible gene expression and this process is dependent on Arnt. However we suggest HIF-1α is not involved insulin-induced gene expression and insulin- and hypoxia- induces same target genes via different signaling pathway. [*This study was supported by a grant 1999-1-209-003-3 from the Korea Science and Engineering Foundation*]