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## INSULIN AND HYPOXIA INDUCE VEGF AND GLYCOLITIC ENZYMES VIA DIFFERENT SIGNALING PATHWAYS

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Both hypoxia and insulin induce same target genes including vascular endothelial growth factor (VEGF), glycolytic enzymes and glucose transporters. However these two signals eventually trigger quite different metabolic pathways. Hypoxia induces glycolysis for anaerobic ATP production, while insulin increase glycolysis for lipogenesis and energy storage. Hypoxia-induced gene expression is mediated by Hypoxia-inducible Factor1 (HIF-1) that consists of HIF-1  $\alpha$  and  $\beta$  subunit. In contrast to HIF-1  $\beta$  protein, HIF-1  $\alpha$  protein is degraded by ubiquitin-dependent proteasome in normoxia but it is stabilized in hypoxia. Hypoxia induced gene expression is initiated by the stabilization of HIF-1  $\alpha$  subunit. Here, we investigated whether insulin-induced gene expression also requires stabilization of HIF-1  $\alpha$ . Our results indicate that hypoxia but not insulin stabilizes HIF-1  $\alpha$  protein, whereas both insulin and hypoxia-induced gene expression require the presence of HIF-1  $\beta$  subunit. Insulin induced gene expression is inhibited by presence of PI3 kinase inhibitor, LY294002 (25  $\mu$ M) and Akt-dominant negative mutant, whereas hypoxia-induced gene expression is not. Furthermore, ROS inhibitors, DPI and PDTC affect insulin-induced gene expression but not hypoxia-induced gene expression. Our results demonstrate that insulin and hypoxia induce same target genes in different pathways.