

P004 High glucose activates hypoxia inducible factor 1 alpha (HIF1 α) and HIF2 α in cultured rat β -cells

Mohammed Bensellam and Jean-Christophe Jonas

Unit of Endocrinology and Metabolism, Faculty of Medicine, Université catholique de Louvain, Brussels, Belgium

Background: We previously reported that the mRNA levels of most glycolytic enzymes and other HIF target genes are markedly up-regulated in rat islets cultured in 30mM glucose (G30) instead of G5.

Hypothesis: High glucose, which increases O₂ consumption in β -cells, may induce hypoxia and thereby cause glucotoxicity.

We therefore tested whether overnight culture in high glucose activates HIF in whole rat islets and INS1-cell monolayer.

Results: High glucose significantly increased the protein levels of HIF1 α , HIF2 α and their dimerization partner HIF1 β (ARNT) in INS1-cell nuclear extracts, and up-regulated HIF target gene mRNA levels (*Gapdh*, *AldoA*, *LdhA*, *Adrenomedullin*). These glucose effects, which were confirmed in rat islets, were mimicked by 6h exposure to a low pO₂ (1%) or by 18h treatment with 100 μ M CoCl₂, a known activator of HIF. In contrast, they were inhibited by a high pO₂ (60%), siRNAs directed against both HIF α isoforms, or agents that reduce the glucose stimulation of β -cell O₂ consumption by inhibiting Ca²⁺ influx and insulin secretion (diazoxide, nimodipine).

Conclusion: Our results suggest that high glucose triggers hypoxia not only in whole rat islets but also in INS1-cell monolayer. The role of hypoxia in *in vitro* β -cell glucotoxicity merits further investigation.