

## Scientific Paper:

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# Role of hypoxia in obesity-induced disorders of glucose and lipid metabolism in adipose tissue

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### Abstract:

Recent studies suggest that adipose tissue hypoxia (ATH) may contribute to endocrine dysfunction in adipose tissue of obese mice. In this study, we examined hypoxia's effects on metabolism in adipocytes. We determined the dynamic relationship of ATH and adiposity in ob/ob mice. The interstitial oxygen pressure ( $P_{O_2}$ ) was monitored in the epididymal fat pads for ATH. During weight gain from 39.5 to 55.5g,  $P_{O_2}$  declined from 34.8 to 20.1 mmHg, which are 40–60% lower than those in the lean mice. Insulin receptor- $\beta$  (IR $\beta$ ) and insulin receptor substrate-1 (IRS-1) were decreased in the adipose tissue of obese mice, and the alteration was observed in 3T3-L1 adipocytes after hypoxia (1% oxygen) treatment. Insulin-induced glucose uptake and Akt Ser473 phosphorylation was blocked by hypoxia in the adipocytes. This effect of hypoxia exhibited cell type specificity, as it was not observed in L6 myotubes and  $\beta$ TC6 cells. In response to hypoxia, free fatty acid (FFA) uptake was reduced and lipolysis was increased in 3T3-L1 adipocytes. The molecular mechanism of decreased fatty acid uptake may be related to inhibition of fatty acid transporters (FATP1 and CD36) and transcription factors (PPAR $\gamma$  and C/EBP $\alpha$ ) by hypoxia. The hypoxia-induced lipolysis was observed in vivo after femoral arterial clamp. Necrosis and apoptosis were induced by hypoxia in 3T3-L1 adipocytes. These data suggest that ATH may promote FFA release and inhibit glucose uptake in adipocytes by inhibition of the insulin-signaling pathway and induction of cell death.

Key-words: abdominal obesity, insulin sensitivity, high-fat diet, hypoxia-inducible factor 1 $\alpha$ , glucose transporter 1