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OBESITY

GLYPICAN-4: ROLE IN INSULIN SIGNALLING

Glypican-4, a novel adipokine, interacts with the insulin receptor (IR) and influences insulin signalling. Investigators from Boston and Leipzig demonstrated that glypican-4 is secreted from white adipose tissue and enhances insulin sensitivity in mice.

Glypican-4 is ordinarily a membrane-bound hormone, owing to a glycosylphosphatidylinositol (GPI) anchor. However, this anchor can be cleaved, allowing glypican-4 to be secreted. The researchers have previously shown that glypican-4 is differentially expressed in visceral and subcutaneous adipose tissue of mice and humans. In the new study they show that expression of this adipokine and its serum concentration in humans are dependent upon BMI and insulin sensitivity.

The investigators found that cultured murine preadipocytes lacking glypican-4 failed to differentiate into adipocytes or to accumulate fat when stimulated to do so with a standard cocktail of drugs. Closer investigation revealed that induction of key adipogenic transcription factors such as PPAR-γ and C/EBPα was disrupted. However, when glypican-4 expression was restored, differentiation was rescued and expression of these key transcription factors was increased. This effect was independent of the integrity of the GPI anchor, indicating that glypican-4 can influence adipogenesis in both its membrane-bound and secreted forms.

Glypican-4 appears to exert its effects by influencing insulin signalling. The research team found that glypican-4 associates with the IR and that insulin stimulation of IR phosphorylation was reduced by 33% in preadipocytes lacking glypican-4 in comparison with control cells. The team also found that low serum levels of glypican-4 were associated with insulin resistance in humans.

Insulin resistance is characterized by a drop in circulating insulin levels. Cleavage of the GPI anchor might be regulated by insulin and so, during development of insulin resistance, insulin and glypican-4 levels would both fall. This compound effect might accelerate disease progression. Maintaining serum levels of glypican-4 in people with insulin resistance or diabetes mellitus could, therefore, reduce their need for insulin therapy.

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Original article Ussar, S. *et al.* Glypican-4 enhances insulin signaling via interaction with the insulin receptor and serves as a novel adipokine. *Diabetes* doi:10.2337/db11-1395