Effect of troglitazone on tumor necrosis factor alpha and transforming growth factor beta expression and action in human adipocyte precursor cells in primary culture.

Abstract:
Troglitazone is a member of the class of thiazolidinediones that are known to act as insulin-sensitizing agents. Administration of these compounds ameliorates insulin resistance in type 2 diabetic patients, but may also promote weight gain. The main site of action is adipose tissue, where troglitazone binds to and activates the nuclear receptor peroxisome proliferator-activated receptor gamma2. The aim of this study was to investigate whether troglitazone is able to affect the adipose expression and function of tumor necrosis factor alpha (TNF-alpha) and transforming growth factor beta (TGF-beta). Both TNF-alpha and TGF-beta blocked adipose differentiation in vitro and led to a marked reduction in glycerol-3-phosphate dehydrogenase activity, a marker enzyme of adipose differentiation, by 69% +/- 11% and 75% +/- 15%, respectively. Addition of 2 mumol/L troglitazone significantly reduced this inhibitory effect of both cytokines on glycerol-3-phosphate dehydrogenase activity. Peroxisome proliferator-activated receptor gamma messenger RNA (mRNA) was reduced by TNF-alpha in freshly isolated adipocytes. This effect was completely counteracted by troglitazone, whereas TGF-beta had no immediate effect on peroxisome proliferator-activated receptor gamma mRNA. Moreover, troglitazone alone promoted adipose differentiation in a time- and dose-dependent manner.
Troglitazone treatment was found to result in a marked reduction of TNF-alpha mRNA expression in human preadipocytes to 54% +/- 13% compared with untreated cultures. Furthermore, troglitazone was observed to partially antagonize the inhibitory effect of TNF-alpha on insulin-stimulated 2-deoxy-glucose uptake in newly differentiated human fat cells. In conclusion, troglitazone exerts a potent adipogenic activity in human preadipocytes, which may be mediated by suppression of the endogenous production of TNF-alpha and by counteracting the antiadipogenic effect of TGF-beta. In addition, troglitazone improved insulin-stimulated glucose uptake in differentiated fat cells.