6. Abstract

The nuclear transcription factor peroxisome proliferator-activated receptor γ (PPARγ) is a central regulator of insulin- and glucose metabolism. PPARγ activation by synthetic ligands, the thiazolidinediones, results in insulin sensitization, thereby preventing and improving the diabetic condition. Angiotensin type 1 receptor (AT_1) antagonists have been shown to reduce the incidence of type 2 diabetes mellitus by an unknown molecular mechanism. We investigated the regulation of PPARγ- mediated fat cell differentiation by AT_1- antagonists and characterized interactions of these compounds with the transcription factor.

AT_1- antagonists enhanced the differentiation of 3T3- L1 and human preadipocytes in a concentration dependent manner. Telmisartan and irbesartan exhibited the most potent impact whereas eprosartan failed to show any effects. An increase in the transcriptional activity of PPARγ induced by theses compounds was independent of their AT_1- blocking property and of the presence of the AT_2- receptor. The induction was achieved by a direct interaction of AT_1- antagonists with the PPARγ- ligand binding domain, which correlated with the impact on fat cell differentiation rendering these compounds as partial agonists in comparison with the thiazolidinediones. Studying protein- protein interactions showed a direct binding of AT_1- antagonists to the PPARγ- ligand binding domain and a selective recruitment of cofactors. Analysis of gene expression profiles revealed a large overlap of similar regulated genes, but also a subset of differentially regulated genes in regard to fat cell function. Consistent to their PPARγ- activating efficacy, they increased the insulin dependent and independent glucose uptake in 3T3-L1 adipocytes.

This work identified certain AT_1- antagonists as partial PPARγ- agonists. The activation of PPARγ demonstrates new pleiotropic actions of certain AT_1- antagonists providing a potential mechanism for their insulin-sensitizing/ anti-diabetic effects. Furthermore, they exhibit a lead structure to develop new PPARγ- modulators.