

Liver-Specific PPAR α -Target Gene Regulation by the Angiotensin Type 1 Receptor Blocker Telmisartan

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ABSTRACT

Objective: The angiotensin type 1 receptor blocker (ARB) and PPAR γ -modulator telmisartan has been recently demonstrated to reduce plasma triglycerides in non-diabetic and diabetic hypertensive patients. The present study investigates the molecular mechanisms of telmisartans hypolipidemic actions, in particular its effect on the PPAR α pathway.

Research Design and Methods: Regulation of PPAR α -target genes by telmisartan was studied by real-time PCR and Western immunoblotting *in-vitro* and *in-vivo* in liver/ skeletal muscle of mice with diet-induced obesity (DIO). Activation of the PPAR α -ligand binding domain (LBD) was investigated using transactivation assays.

Results: Telmisartan significantly induced the PPAR α target genes carnitine palmitoyl transferase 1A (CPT1A) in human HepG2 cells and acyl-CoA synthetase long-chain family member 1 (ACSL1) in murine AML12 cells in the μ -molar range. Telmisartan-induced CPT1A stimulation was markedly reduced after siRNA-mediated knockdown of PPAR α . Telmisartan consistently activated the PPAR α -LBD as a partial PPAR α agonist. Despite high *in-vitro* concentrations required for PPAR α activation, telmisartan (3mg/kg/d) potently increased ACSL1 and CPT1A expression in liver from DIO-mice associated with a marked decrease of hepatic- and serum triglycerides. Muscular CPT1B expression was not affected. Tissue specificity of telmisartan-induced PPAR α -target gene induction may be the result of previously reported high hepatic concentrations of telmisartan.

Conclusions: The present study identifies the ARB/ PPAR γ modulator telmisartan as a partial PPAR α agonist. As a result of its particular pharmacokinetic profile, PPAR α activation by telmisartan seems to be restricted to the liver. Hepatic PPAR α activation may provide an explanation for telmisartan's anti-dyslipidemic actions observed in recent clinical trials.

Angiotensin type 1 receptor blockers (ARBs) are commonly used in the treatment of hypertension and related cardiovascular end organ damage (1). Recently a distinct subgroup of ARBs has been identified as partial agonists for the peroxisome proliferator-activated receptor γ (PPAR γ) with selective PPAR γ modulating properties. (2-4). In contrast to full glitazone agonists, PPAR γ -activating ARBs exert selective recruitment of nuclear cofactors resulting in *in-vivo* insulin sensitization in the absence of weight gain in obese insulin resistant mice. (3) Among the ARBs telmisartan has been shown to be the most potent PPAR γ modulator. (3; 4) Based on these *in-vitro* results and data from animal experiments a number of clinical studies have been conducted where the metabolic actions of the PPAR γ -activating ARB telmisartan have been intensively investigated. (5-9) When compared to ARBs which do not exert PPAR γ -activating properties, telmisartan not only improves insulin sensitivity but also induces beneficial actions on serum lipid levels such as a reduction of serum triglycerides. (5; 10; 11)

PPARs are ligand-activated transcription factors belonging to the superfamily of nuclear receptors. PPAR γ is abundantly expressed in adipose tissue and a major regulator of insulin- and glucose metabolism. (12) In contrast, PPAR α is highly expressed in tissues displaying a high metabolic rate of fatty acids (FA) such as the liver and skeletal muscle. (13) PPAR α modulates intracellular lipid metabolism by transcriptional regulation of genes involved in FA-uptake, mitochondrial FA-oxidation, and triglyceride catabolism. (13; 14) Natural PPAR α ligands comprise mono- and polyunsaturated FAs as well as eicosanoids. (15) In addition, PPAR α is also the molecular target of the lipid-lowering fibrates such as gemfibrozil, bezafibrate, clofibrate and fenofibrate. These substances

are used to treat dyslipidemia and cardiovascular disease. (13; 15)

It has been reported that certain PPAR γ activators such as pioglitazone are also able to activate PPAR α . Furthermore, it has been proposed that the positive actions of pioglitazone on diabetic dyslipidemia might at least in part be mediated by its PPAR α -activating abilities. (16; 17) To understand the underlying mechanism of telmisartan's lipid-lowering actions we studied the effect of telmisartan on major PPAR α -target genes involved in FA-oxidation in the human hepatoma cell line HepG2, the murine hepatic cell line AML12, and in liver/skeletal muscle of diet-induced obese mice treated with telmisartan. Furthermore, activation of the PPAR α -ligand binding domain (LBD) and regulation of PPAR α protein-/ mRNA-expression by telmisartan was studied.

The present study demonstrates that telmisartan induces the PPAR α target gene carnitine palmitoyl transferase 1 (CPT1A) in HepG2 cells and acyl-CoA synthetase long-chain family member 1 (ACSL1) in AML12 cells. Consistently, telmisartan acts as a partial PPAR α agonist in PPAR α transactivation assays and induces PPAR α expression. High-fat diet fed mice treated with telmisartan showed a pronounced induction of hepatic ACSL1 and CPT1A which was associated with a significant decrease of hepatic- and serum triglycerides. Interestingly, CPT1B expression in skeletal muscle was not affected by telmisartan. Tissue specificity of telmisartan-induced PPAR α -target gene induction may result from high hepatic telmisartan concentrations which have been documented in rodents during early preclinical studies. (18)

In summary, the present study identifies the ARB telmisartan as a partial PPAR α agonist. Based on its specific pharmacokinetic profile, PPAR α activation by telmisartan appears to be liver-specific. Hepatic induction of PPAR α -target genes

