Pleiotropic effects of thiazolidinediones: Taking a look beyond antidiabetic activity

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ABSTRACT. Thiazolidinediones (TZD) [Troglitazone (TRO), Pioglitazone (PGZ), Rosiglitazone, (RGZ)] are a novel class of antidiabetic drugs for patients with Type-2 diabetes mellitus (T2DM) able to decrease blood glucose, working through a reduction of insulin resistance. The family of TZD exerts its effect specifically bound to peroxisome proliferator-activated receptor γ (PPARγ). This is a member of the nuclear hormone receptor superfamily of ligand-dependent transcription factors, together with PPARα and δ. Although PPARγ is essentially expressed in adipose tissue, it has also been found in endothelial cells, macrophages, vascular smooth muscle cells, glomerular mesangial cells, hepatic stellate cells and in several cancer cell lines. In these cells, the PPARγ activation by TZD determines modulatory effects on growth factor release, production of cytokine, cell proliferation and migration, extracellular matrix remodeling and control on cell cycle progression and differentiation. In addition, TZD have been shown to have a potent antioxidant effect. This review, taking a quick look beyond the antidiabetic activity of PPARγ, shows the dramatic ranging of medical implications that the use of TZD could have modulating the PPARγ activity in several diseases with a strong social impact, such as insulin resistance syndrome, chronic inflammation, atherosclerosis and cancer.

INTRODUCTION

Peroxisome proliferator-activated receptors (PPAR) are members of the nuclear receptor superfamily. Three subtypes - PPARα, PPARδ and PPARγ - have been identified with distinct tissue distribution and biological activities. PPARα is present in liver, heart, muscle and kidney, where it regulates fatty acid metabolism. PPARγ is highly expressed in the adipocytes and macrophages and controls the adipocyte differentiation, lipid storage and glucose homeostasis. PPARδ is expressed in a variety of tissues with less definite functions.

The human PPARγ gene is composed of 9 exons spanning more than 100 Kb of genomic DNA on chromosome 3 p 25 in the proximity of the locus of the retinoic acid receptor (3 p 24) and thyroid hormone receptor β (3 p 21). In humans, 3 PPARγ isoforms (γ1, γ2, γ3), generated by alternative splicing, have been identified; and four major domains have been characterized. The proteins having a N-terminal domain (AB), which differ in both length and predicted amino acid sequence, contain a ligand independent transactivation domain called activation function 1 (AF1). This domain plays an important role in regulating PPAR activity through both phosphorylation and interdomain communication. The proteins also contain a DNA binding domain (C) with high homology (≥80%) among the family members and a ligand-binding domain (D, E, F), which is located at C-terminus and share about 65% of homology among the family members. This last domain contains a second transactivation domain (AF2) (Fig. 1). The less conserved ligand-binding domain permits each PPAR to have its own specific ligands. PPAR receptors heterodimerize with retinoic acid X receptor (RXR) and regulate the transcription of target genes through binding to specific response elements (1). Although levels of expression of PPARγ are low in muscle (<10% of the levels present in the...
adipose tissue), obesity is associated with elevated PPARγ expression in muscle. In contrast to white adipose tissue, PPARγ does not appear to be regulated by insulin in muscle. However, the treatment with PPARγ agonists induces an increase of PPARγ mRNA in muscle (2). PPARγ is bound and activated by several naturally occurring compounds, such as 15-deoxy-D_2,14-prostaglandin J2, leukotriene B4 as well as a number of synthetic molecules (1). Among them, the most interesting for the endocrinologists are the TZD, because of their antidiabetic activities.

**PPARγ agonists and glucose metabolism**

TZD have been developed and approved for treatment of insulin resistance and diabetes mellitus. However, only pioglitazone (PGZ) (©Actos) and Rosiglitazone (RGZ) (©Avandia) are currently available for clinical purposes. These drugs improve insulin sensitivity as clearly demonstrated by euglycemic hyperinsulinemic clamp (3). The mechanism remains elusive: the muscle is the major tissue accounting for up to 85% of insulin stimulated glucose disposal, but the PPARγ receptors are highly expressed in fat, little in liver and very little in muscle (1). TZD induce an increase of glucose transporter 4 (GLUT 4) in adipocytes but, because the adipose tissue is responsible for < 5% of total glucose disposal, this increase of GLUT 4 alone cannot explain the profound drug activity. Thus, other mechanisms should be taken into account. Since free fatty acids determine insulin resistance in muscle, TZD sequestering the lipids into fat stores should reduce the metabolic burden to the liver and muscles and improve insulin sensitivity and glucose use. In addition, TZD in the adipose tissue down-regulate leptin, TNFα and resistin. All these adipokines are antagonizing the effects of insulin at the target tissues. On the contrary, TZD have been demonstrated to increase the production of adiponectin, which improves insulin sensitivity (4) (Fig. 2). PPARγ activation also appears to increase glucose oxidation in the muscle and to decrease glucogenesis in the liver, in spite of the fact that these effects only occur when higher concentrations are reached. Confirming data of their “insulin-sensitizer role” come from some clinical observations, where TZD are also effective in ameliorating insulin resistance in conditions that are not associated with frank diabetes but are characterized by insulin resistance, such as the plurimetabolic syndrome, obesity and polycystic ovary syndrome (4).

It has been reported that a mutation in the ligand-binding domain of PPARγ induces insulin resistance diabetes and hypertension. In the PPARγ structure, the mutation destabilizes helix 12, which mediates transactivation. As a consequence of this, the receptor mutants are strongly transcriptionally impaired and able to inhibit the action of co-expressed wild-type PPARγ in a dominant negative manner (5). These findings clearly demonstrated that PPARγ is important in the physiological control of insulin sensitivity, glucose metabolism and hypertension.

As mentioned before, TZD have been classified as “insulin sensitizers”. Thus, these drugs, in general,