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Review

Effects of Thiazolidinediones on metabolism and cancer: Relative influence of PPARγ and IGF-1 signaling

Amreen Mughal [a], Dinesh Kumar [b], Ajit Vikram [c,*]

[a] Department of Pharmaceutical Sciences, North Dakota State University, Fargo, ND, USA
[b] Department of Chemistry and Biochemistry, North Dakota State University, Fargo, ND, USA
[c] Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, IA, USA

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ABSTRACT

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor-gamma (PPARγ) agonists. TZDs are orally effective medicines for metabolic syndrome and type 2 diabetes. In addition to metabolic effects these molecules also possess anti-cancer effects. Data from diabetes clinical trials also support anti-cancer effects of TZDs. The anti-cancer effects of TZDs neither correlate well with their ability to activate PPARγ receptor, nor are affected by the presence of PPARγ receptor antagonists. Accumulating evidence suggests that TZDs act as selective inhibitors of insulin-like growth factor-1 (IGF-1) receptor signaling, and IGF-1 signaling is known to be aberrantly regulated in various cancers. Structural analysis of TZDs suggest that the presence of 5-exo C–C single bond of the thiazolidine-2,4-dione ring is important for the metabolic effects but not for anti-cancer effects, as inclusion of C=C double bond at this position promotes antagonistic properties to the PPARγ receptor without compromising its anti-proliferative effects. The objectives of this review includes summarization of the relative influence of TZDs on PPARγ and IGF-1 signaling in mediating pharmacological effects, and to discuss the possibility of multiple pharmacophores, and thereby independent regulation of PPARγ and IGF-1 signaling.

Contents

1. Introduction

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor-gamma (PPARγ) agonizts and were initially developed to improve lipid lowering effects of fibrates, e.g. clofibrate, fenofibrate, but were later identified to have glucose and lipid lowering effects through a distinct mechanism, PPARγ receptor activation. PPARγ1, a PPARγ receptor subtype, has a broader distribution including liver, skeletal muscle, lung and intestine, while PPARγ2, another subtype, is mainly present in the adipose tissue (Michalik et al., 2006; Proks et al., 2002). TZDs improve sensitivity to the insulin and are known as insulin-sensitizers. Although, these potent insulin-sensitizers are effective oral medication for type 2 diabetes, the unique benefits are abated by the risk for fluid retention, weight gain, bone loss and heart failure. In the last two decades of the 20th century multiple TZDs have been introduced as anti-diabetic agents but most of them were withdrawn owing to

* Corresponding author.
E-mail address: ajitvikram@gmail.com (A. Vikram).

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the risk of hepatotoxicity or myocardial infarction. Pioglitazone, the most widely used TZD, regulates adipocytes differentiation and fat redistribution, resulting in the decreased visceral (Miyazaki et al., 2002) and hepatic (Vikram et al., 2010) fat. These effects underscore wide-spread long term use of pioglitazone for the treatment of metabolic syndrome and type 2 diabetes (Salomone, 2011).

The serendipitous discovery of anti-cancer properties of TZDs (Elstner et al., 1998; Koeffler, 2003) added another dimension to their potential use, especially for the insulin-resistant individuals suffering from various types of cancer, but raised safety concerns. Interestingly, both PPARγ receptor agonists as well as antagonists induce apoptosis in cancer cells irrespective of the cellular expression of PPARγ receptors (Shiau et al., 2005). A recent study suggests that anti-proliferative effects of TZDs are linked with relative expression of PPARγ and testicular receptor 4 (TR4) in the prostate cancer (Lin et al., 2015). Another concern regarding the use of TZDs was the higher occurrences of bladder cancer in patients treated with pioglitazone (Dormandy et al., 2009, 2005; Jin et al., 2014). In a recent cohort involving 193,099 individuals the use of pioglitazone was examined for its association with the bladder and 10 other cancers, and the results suggest no statistically significant association but an increased risk cannot be excluded. The study indicated an increased risk for prostate and pancreatic cancer but suggested further investigation (Lewis et al., 2015). The use of TZDs is expected to rise due to the increased toll of metabolic syndrome across the globe. The association between pioglitazone and bladder cancer (Dormandy et al., 2009, 2005; Jin et al., 2014), especially in absence of better alternatives for the management of type 2 diabetes, provides space to re-examine the risk to benefits ratio of TZDs.

Aberrant IGF-1 signaling has been identified in several cancers (Pollak, 2012) and TZD analogs have recently been identified as potent inhibitors of IGF-1 receptors (Liu et al., 2010). Although, limited information is available about the regulation of IGF-1 signaling by TZDs, based on present evidences TZDs appear to negatively regulate IGF-1 signaling at multiple nodal points. The inhibition of pro-survival IGF-1 receptor signaling by TZDs may partially explain the observed anti-cancer effects of TZDs. The understanding of anti-cancer effects of TZDs still remains elusive and a careful re-examination of its chemistry and pharmacological effect is needed. This review is aimed to understand the current status and concerns associated with TZDs, its relative influence on PPARγ and IGF-1 signaling, and to analyse the possible presence of multiple pharmacophores.

2. Brief history and current status of TZDs

Diabetes mellitus (type 2) is a metabolic disorder associated with impaired glucose disposal primarily due to reduced insulin-receptor signaling. Until the discovery of insulin, the most effective way for the treatment of diabetics remained the dietary restrictions with minimal carbohydrate intake, which had hardly improved the life-expectancy and quality of life. Effective treatment of diabetes emerged in 1921 with the discovery of insulin (Rosenfeld, 2002). Several categories of drugs were discovered during the mid 1900s including sulphonylureas (Proks et al., 2002) and biguanides (Goodarzi and Bryer-Ash, 2005). Sulphonylureas bind with ATP-sensitive potassium (K_{ATP}) channels and stimulates insulin secretion from pancreatic β-cells (Proks et al., 2002). However, the patients with pancreoprivic diabetes, or later stages of type 2 diabetes, do not respond to these medications and these can also result into detrimental hypoglycaemia (Riddle, 2005). Biguanides primarily impair hepatic gluconeogenesis through a mild and transient inhibition of the mitochondrial respiratory-chain complex 1 (Viollet et al., 2012) but these molecules induced lactic acidosis and resulted in an increased death tolls (Luft et al., 1978). The increased disease incidences, unsatisfactory performance in terms of glycaemic control, and associated side effects fueled search for better alternatives. In a similar timeframe (1950s–1960s) fibrates were identified to have a lipid lowering effect (Cottet et al., 1953; Mathivat and Cottet, 1953). TZDs were initially developed in an attempt to synthesize potent fibrates, and many analogs showed both hypoglycemic and hypolipidemic effects (Kawamatsu et al., 1980a, 1980b), marking a new era of active search for safer and effective TZDs. In 1980, Takeda Pharmaceuticals (Japan) brought Ciglitazone (Fujita et al., 1983), followed by Troglitazone by Sankyo Pharmaceuticals, Japan (Fujiwara et al., 1988). Identification of liver toxicity with use of troglitazone triggered efforts to identify better insulin-sensitizers. In the 1990s, pioglitazone and rosiglitazone were added to the category, and at present, they are the only TZDs used for the treatment of type 2 diabetes. Rosiglitazone was considered a blockbuster anti-diabetic medicine with a steep rise in market share. None the less, cardiac failure and myocardial infarction cases caused US prescription restriction and European Union (EU) market withdrawal in 2011. However, in November 2013 FDA removed the restriction on rosiglitazone considering the findings from **R**osiglitazone **E**valuated for **C**ardiovascular **O**utcomes and **R**egulation of Glycemia in **D**iabetes (RECORD) trial which proposed no risk of heart failure with the use of rosiglitazone but it continues to remain unavailable in the EU and New Zealand. In recent years, pioglitazone use was reported to increase the risk of bladder cancer (Dormandy et al., 2009, 2005; Jin et al., 2014), and several countries including France, Germany, Tunisia and Mauritius suspended the use of pioglitazone in new patient population (Tseng, 2012). European Medicines Agency (EMA) considered the associated risk and suggested that due to unavailability to better alternatives, the drug can be used as a second line of treatment (Agency, EMA, 2011).

3. Mechanism of action of TZDs on PPARγ

PPARγ receptors are non-steroid nuclear receptor which consists type II zinc finger DNA binding motif and hydrophobic ligand binding pocket (Chandra et al., 2008). The binding of TZDs with PPARγ receptor (NR1C3) results in the conformational change and activation of the PPARγ receptor (Berger et al., 1996). The binding of partial or full agonist to PPARγ receptor triggers stabilization of the PPARγ receptor-retinoid X-receptor (RXR) heterodimer and promotes recruitment of the co-activators. The PPARγ receptor along with co-activators regulates expression of genes harboring PPAR response elements [PPRE] (Ahmadian et al., 2013; Rogue et al., 2011, 2010). In absence of ligand, PPARγ receptor-RXR heterodimer forms a complex with the corepressor proteins, e.g. NCoR and SMRT, and thereby minimizes the PPAR-mediated transcription of genes. TZDs regulate expression of network of genes involved in adipogenesis, inflammation, insulin-signaling and lipid metabolism (Berger and Moller, 2002). In general PPARs are known as receptor for the dietary fatty acids but they also bind and respond to prostaglandins and oxidized phospholipids (Forman et al., 1996).

PPARγ receptors are highly expressed in the lipid accumulating cells such as adipocytes, tissues macrophages and aortic foam cells which play an important role in the pathogenesis of diseases including obesity, type 2 diabetes and atherosclerosis, which makes them a particularly interesting pharmacological target for these diseases. TZDs have dual effects on the adipocytes which include; direct promotion of cellular uptake and storage of fatty acids in adipose tissues, and refractory insulin sensitization through adipokines release (adiponectin